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American Gynecological Society
Transactions of the Seventy-eighth Annual Meeting
Quebec, May 23-25, 1955

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American Journal of Obstetrics and Gynecology

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American Gynecological Society

Transactions of the Seventy-eighth Annual Meeting
Quebec, May 23-25, 1955

A BOOK REVIEW: SAMUEL BARD'S "A COMPENDIUM OF THE THEORY AND PRACTICE OF MIDWIFERY"*

Presidential Address

PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

THE addresses of my presidential predecessors have covered so many phases of our specialty, as well as biography, history, philosophy, and even prose poetry, that I have been perplexed to find an untouched subject. Then the exacting but interesting occupation of my spare hours over a period of many years obtruded so strongly that I have chosen to present you with a book review.

For this I have selected Samuel Bard's *Compendium of Midwifery,* the first obstetrical text written by an American author and published in the United States.

Samuel Bard was born in Philadelphia in 1742.[1] When a boy, he removed to New York with his physician father, and was educated at King's College. Early in 1762 he sailed for Edinburgh. His ship was captured by privateers and he spent five months in a French prison from which Benjamin Franklin effected his release. He served that summer, 1762, as a house pupil at St. Thomas's Hospital, going down to Edinburgh a month before the Medical School opened "to become familiar with the Scottish pronunciation of Latin." He received his degree in 1765 after defending his thesis, "De Viribus Opii," before Cullen and the two Munros.

Bard was no doubt a student of Thomas Young, then Professor of Midwifery, but he does not refer to any of Young's principles in his book. After

*Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

returning to New York, he entered practice with his father, and founded both the Medical School of King's College and the New York Hospital. John Morgan, who founded the Medical School of the College of Philadelphia, and Samuel Bard, who founded the Medical School of King's College, began a lifelong friendship while students at Edinburgh. The characters and the abilities of this Scottish faculty must have been of great influence on these two students to have stimulated them to establish medical schools in their home cities almost immediately after their return to the Colonies.

On the opening of the new Medical School at King's College, Bard was the first Professor of Physic. After the untimely death, in 1770, of Tennent, the original holder of the chairs of Materia Medica and Midwifery, the latter title was assumed by Bard until the school closed in 1776. Later he was Professor of Chemistry and Natural Philosophy in the new school; then in 1792 became Dean of the Medical School of Columbia College, and finally, President of the College of Physicians and Surgeons in the University of the State of New York. His executive ability and civic leadership were amply recognized and fully utilized.

Dr. Bard retired from practice to his estate at Hyde Park in 1799. Here he began to write a compendium of Midwifery, his favorite branch of medicine for over thirty years, in which he had enjoyed a high reputation. The work was titled *A Compendium of the Theory and Practice of Midwifery,* described in the subtitle as "Containing Practical Instructions for the Management of Women During Pregnancy, in Labour, and in Child-bed: Calculated to Correct the Errors and to Improve the Practice of Midwives; As Well as to Serve as an Introduction to the Study of This Art for Students and Young Practitioners." The book was published by Collins and Perkins of Pearl Street, New York, 1808. The first printing was incorrectly dated 1807. It was reprinted in a short time and subsequent editions appeared in 1812, 1814, 1817, and 1819.

In an eighteen and a half page introduction Bard states his motive for writing the book, "Having frequently observed how much our midwives and too many practitioners who take on themselves the care of women stand in need of instruction, and how incapable most of them are to derive it from systems of midwifery, I have thought that a concise, cheap book with plain but correct rules for practice in normal labours would prove a useful work."

Bard states, "I have attempted to be useful, to say nothing but what is absolutely necessary and easily understood; and to recommend such practices as have received the stamp of time and experience, rather than to offer new opinions." He further relinquishes all claims to originality, and frankly confesses he has used the language of others where it clearly served his purpose. He continues refreshingly, "Being convinced that the use of instruments by unskillful men is more dangerous than the most desperate case left to nature, I wished to avoid as much as possible even mentioning these operations, and stressed the great resources of nature."

Acknowledgments having been made to various English and Scottish authors and to Baudelocque, Bard writes, "It may appear singular that in this

enumeration of authors I have not mentioned Smellie,[2] whose works are in the hands of almost every practitioner in this Country and more generally read than any other. But, although a great improver of the art of Midwifery, Smellie certainly was not acquainted with all the resources of nature in their full extent."

In concluding his rather over-long introduction, Bard admonishes "every young person engaging in a study of Midwifery not to trust wholly to books since so much depends on that which is to be learned from practice." Antedating our system of internships and residency programs he advises such young persons "to spend one or two sessions in one of the medical colleges where he may have an opportunity to add experience to theory."

After an acceptable description of the normal pelvis passed down from earlier anatomists, Bard discusses the deformities to be met, their causes, and their obstetric significance. He ascribes the majority of pelvic deformities to three etiologies; psoas ulcer (caries of the lumbar vertebrae), rickets in childhood, and malacosteon (mollities ossium). In the prevention of rickets he advocates sunlight and a good diet; the condemnation of child labor, and a healthy adolescence. The third etiological factor he regards as usually progressive. Noting the high maternal mortality associated with destructive operations often necessary to deliver deformed women in those pre-cesarean days, Bard suggests that every such deformed woman, especially if lameness be associated, should consider the risk she would run by engaging in marriage, and should submit to a proper examination before she determined to purchase the title of mother at so dear a possible risk. Here was an early and worthy recommendation of premarital and preconceptional examination.

According to Englemann[3] this period was fruitful of many valuable studies on the physiology of the sex organs. Bard was cognizant of most of these advances and notes the experiments of such investigators as Leuwenhoek, Spallanzi, Hunter, and Bell. He cites an experiment with female rabbits during estrus; if penned with a male but without access to him, the ova of such rabbits were found not only congested and enlarged but actually burst from their cells. He transposes this psychosomatic stimulus to the human as follows: "In the ovaries of a young woman who from the circumstances of an imperforate hymen and restraint, there was the strongest reason to believe had had no sexual commerce with men, but who was probably of a warm constitution and had indulged in lascivious practices, hair, teeth, bones and other signs of an imperfect conception were discovered." One must regard this as an original explanation of an ovarian teratoma.

Bard felt that the human female furnished "the ovum with its membrane, its fluids, the placenta, and the rudiments of the fetus in all its parts; but inert and scheduled to perish, unless stimulated and roused into life and action by the energy of the male semen." Bard agreed with the opinion of John Bell that menstruation, due to the general activity of the whole uterine system and to the increased blood to these parts to prepare them for the function of conception, consisted of a relief from this action when the end for which it was intended had passed. He notes observations on the appearance of the fundal

endometrium during menstruation in women with chronic inversion of the uterus, and ascribes the flow to the contorted peripheral extremities of the arteries. He mentions among the various opinions as to the proximate cause of the flow the existence of a peculiar ferment in the endometrium and that the flow was in the nature of a secretion.

The mechanism of impregnation was a fertile field of thought for the physiologist of Bard's era. Leuwenhoek, Buffon, Harvey, and Haller each had a different theory. Reciting the processes observed in the vegetable world and in some lower animals, the water newt, the frog, and the rabbit, especially the experiments performed on the frog by Spallanzani, Bard argues from analogy that the contact of the semen masculinum and the ovum was necessary for conception. "In the human species" he writes, "although we cannot certainly trace the course of the semen to the ovarium it gets there by a shorter route than that of the circulation."

In an extended discussion of the extrauterine pregnancy Bard denied the possibility of a primary abdominal pregnancy. He cites here a correct preoperative diagnosis of an extrauterine pregnancy, operation, and recovery in the practice of his father, John Bard, in 1759.[4] Superfetation Bard believed possible, citing the oft-quoted case of Dewees; but he observes that in most reported instances the smaller fetus showed evidence of earlier death. The statement occurs in all editions that "it is generally allowed by most anatomists that the ovum does not enter the cavity of the womb before the end of the first month of pregnancy." The established anatomy and generally accepted physiology of the fetal circulation is also described, Bard adding the observations that "the cord has no nerves, a wise provision of nature, by which any direct connection between the feeling and passions of the mother and the nervous system of the fetus and the many injuries that might possibly arise from thence are prevented."

A long chapter is devoted to "Sexual Disease of Women." For the most part this relates to disorders of menstruation and of the menopause. He gives the clinical picture of a cauliflower excrescence, a typical story of progressive invasion, metastasis, and death from carcinoma of the cervix. "Extirpation," Bard says, "serves only to aggravate the complaint." Touching is advised but visual examination is not mentioned.

The diagnosis of pregnancy should not be equivocally stated before the fourth month, the author advises, "when the womb will have risen above the pubis, and a tumor the size of a goose egg will be discovered on vaginal examination." Without the advantages of his patients recording their daily temperature readings, Bard observes, "that a slight fever which requires no particular treatment is a very common sign of early pregnancy."

Retention of urine resulting from the pressure obstruction of a retroverted uterus seems to have been a very frequent complication of early pregnancy in Bard's day. The ultimately successful therapeutic procedure included the administration of a large dose of laudanum followed by venesection until the patient fainted; then, with the unfortunate patient held in the knee-elbow position, to force the fundus forward manually by combined rectal and vaginal pressure.

"Fits" are divided into two groups, those occurring in pregnancy and those associated with labor. The first group is ascribed to "that greater degree of sensibility and irritability by which women are distinguished from men, and which receives a great increase from conception." "Hence at such times," Bard writes, "women are peculiarly likely to nervous, spasmodic and convulsive disease; and hence, too, women who are the inhabitants of populous cities, and in the higher spheres of life, who have been delicately bred and who indulge themselves in dissipated luxurious life, particularly those who indulge in spiritous liquors are much more liable to these dreadful and fatal diseases than the more hardy inhabitants of the country."

"Such convulsions [the term Bard used after the second edition] as occur in the early months of pregnancy partake more of the nature of hysteria," adding at the time of writing, 1817, that "hysteria is unquestionably a less frequent disease than it was fifty years ago, probably due to the fashion of the day." Convulsions which occurred later in pregnancy were regarded as of a mixed nature and were termed "epileptic, but with what propriety," Bard writes, "we know too little of the nature of epilepsy to say." Again, he writes, "the convulsions which occur at the onset or during labour are due to the determination of blood to the head and approach to the nature of apoplexy, and frequently become truly apoplectic."

An excellent description of pre-eclampsia (as we know it) is given, but with the peculiar omission in all the editions of edema as a premonitory sign. The point is emphasized "that if early attention would be paid to the signs and symptoms described they might not only be relieved, but the more dangerous state of convulsions which they threaten would probably be prevented." For treatment, copious and repeated bleeding is recommended with active purgation, together with a low diet and an abundance of cooling drinks. Bed rest was obligatory. Of the use of opium, Bard was apprehensive, except in grave cases, to give time for other remedies to become effective. This is puzzling, since the sedative action of opium, as opposed to a supposedly stimulant one, was the crux of his thesis, "De Viribus Opii," for his degree.

Convulsions during labor, Bard believed, were favored by the increased irritability of the woman, and were precipitated by pressure on the internal os of the forces of labor. Bard points out again the premonitory symptoms and the preventive effect of copious bleedings. He recites the bold treatment of James Hamilton, who bled at the time of the first attack to the tune of forty ounces, and repeated in the same amount at the end of an hour, and had not lost a single convulsive case since adopting this method. If labor had progressed to suitable dilatation of the internal os, turning and extraction were advised; if the head was low in the pelvis, forceps should be used. Bard proscribes forcible dilatation of the cervix to effect delivery, and warns against interfering during the fourth stage. He was of the opinion that early blindness in the attacks, unconsciousness between convulsions, and the postpartum onset pointed toward a fatal outcome.

The distinction, first made by Rigby, between accidental hemorrhage (premature separation of the placenta) and necessary hemorrhage (placenta pre-

via) was adopted by Bard, who felt that the exact diagnosis necessitated an internal examination. As to treatment of either, he asserts "the propriety is to promote delivery by art in all cases of hemorrhage, as soon as the state of the parts will permit." Delay and such palliative measures as bleeding, sedatives, and application of cold should be used, "while awaiting consultation, which the young and inexperienced should always require." Bard regarded "vaginal stuffing" as a dangerous measure in that unrecognized hemorrhage could occur above it to a fatal degree; only in the instances where the internal os was not dilated would he adopt its use in an attempt to induce labor.

If only the membranes were touched, or if but an edge of the placenta presented, the membranes should be ruptured immediately. However, with a placenta located centrally, or nearly so, relaxation by laudanum being obtained, vaginal and cervical dilatation and turning should be performed. Passing the hand through such a placenta Bard recommends as a safer procedure than separating it from the wall of the uterus to reach the feet. The description of dilatation and version is meticulously detailed.

Bard, who was undoubtedly an avid student of Smellie, as well as of Denman and Baudelocque, understood the mechanism of labor thoroughly and described it well. He defines labor as "natural," when the head presented and delivery was accomplished by the effect of nature alone; as "preternatural," when the body was delivered before the head; as "tedious and difficult" when delaying or obstruction situations were present. Four stages of labor are defined; the presently accepted second stage Bard divided into two parts: the first being descent to the pelvic floor and rotation; the second part, (his third stage) being the expulsion of the head and body through the vaginal orifice, which in his text is the external os. The fourth stage comprised the delivery of the placenta. The philosophy of modern obstetrics suggests the adoption of a fourth stage, namely, a period of postdelivery observation, a point well taken in view of the many, albeit often minor, interferences or modulations of normal spontaneous delivery.

Never to interfere if there was normal progress of labor was the cardinal principle laid down by Bard in his rules of conduct. His directions for "touching," the internal examination which he suggests be made early in labor, are explicit, since he believed that a correct diagnosis could be made and proper deductions be drawn only after a thorough examination.

"I condemn as it rightly deserves," he declares, "the abominable practice of boring, scooping and stretching the soft part of the mother under the preposterous idea of making room for the child to pass."

Postmaturity was not a point of concern to Bard. According to him the onset of labor was not caused by the inability of the uterus to expand further or to the uneasiness of its contents, but to a law of nature of which he knew no more the cause, he says, in the language of his hobby, experimental horticulture, "than why strawberries ripen in June and peaches in August."

Regarding the relief of pain in labor, Bard writes, "No skill or art of the attendant or exertion on the part of the woman can in the least contribute either to lessen the severity of the pains or shorten their duration. Large

anodynes must not hastily be had recourse to on every occasion of impatience lest we interrupt those pains which are essential to labour." Antedating the advocates of childbirth without fear, Bard advises, "that Hope and Confidence increase the action of the womb while Fear and Dread retard it. A cheerful behaviour on the part of the accoucheur will do much to dispel the timidity and apprehension which which women are affected at the commencement of labour."

Both the immediate removal of the placenta by manual separation and extraction, and the contradictory practice of leaving the separation and expulsion entirely to nature, as advocated by Dr. William Hunter, were opposed by Bard. He suggested waiting for at least one-half hour for the uterus to regain its contractile state and spontaneously expel the placenta. If, at the end of this period the insertion of the cord in the placenta cannot be touched, the "belly" should be examined. If the womb be soft and flaccid, he directs "that it be taken in the hollow of the hand, raise it up toward its natural position, press it moderately, and rub the surface of the belly over it gently. You will perceive it contract by assuming the form of a ball of considerable hardness. On retracing the cord the placenta will usually be found in the os tincae and may be delivered easily." Cutter regarded the maneuver suggested by Bard as antedating the method of Credé. However, John Harvey, a nephew by marriage of Smellie, published an almost identical technique in 1767.

In opening his discussion of "Tedious and Difficult Labours," Bard admonishes the young and inexperienced "that in such cases his knowledge, patience, humanity, fortitude and integrity will be put to the severest trial and that upon his decisions the lives of two individuals may depend." He again stresses the need for worthy consultation. He particularizes the method of and appreciation of findings on internal examination: the state of the soft parts, the capacity of the pelvis, the position of the head, and the analysis thereof to determine the proper course to be pursued.

The use of ergot in labor is discussed in the third edition. John Stearns'[5] "An Account of the Pulvis Parturiens, A remedy for Quickening Child-Birth," was published in the *Medical Repository* in 1808. Prescott[6] reviewed the subject in 1814. Bard quotes him, "its general effect is to excite one long continued and uninterrupted action of the womb, which may continue for an hour or more, until its contents are expelled, or the energy of the remedy and the strength of the woman exhausted and the child probably destroyed." Bard writes further, "one of the warmest advocates of this remedy in pronouncing its eulogium intimates that no woman need suffer the pains of labour, and no practitioner lose his time in a longer attendance than three hours, and that after such a period he is in the habit of exhibiting the ergot to hasten the labour. A more inconsiderate, dangerous or unjustifiable sentiment cannot be expressed, and I certainly advise him to reconsider and correct it."

It may have been more than a mere coincidence that in the 1817 edition, which appeared shortly after John Stearns' election as President of the Medical Society of the State of New York, Bard deleted his somewhat more than mild disapproval noted above. Bard suggests that ergot be administered only after

complete dilation of the internal os (os tincae), with full knowledge of the presentation of the fetus, and only when the pelvis possessed no insuperable obstacles, and never to a woman who was exhausted in labor. He advised, later in the text, that in hemorrhage after delivery ergot be given a trial.

There is an excellent discussion of such causes of prolonged labor as inertia uteri, rigidity of the soft parts, and large child. One of the frequent criticisms of Smellie's teaching and practice may be quoted here. As an obstacle of the soft parts, Bard was discussing cases of unyielding cervix. "Rigid, perhaps, from disease," he writes, "they refuse to relax under the usual methods. In several such cases Smellie snipped the edge of the orifice with a pair of scissors or a knife; but the event was generally, or I believe always fatal." Although Bard subscribed to rupture of the membranes for indicated induction of labor, he advised the amniotic sac be preserved as long as possible in normal labor. He observes that premature birth was usually associated with long and tedious labor. A latent period of even several weeks following premature rupture of membranes did not disturb him, or overcome his hope of prolonging gestation in favor of greater maturity of the fetus. The possibility of ascending infection was naturally, at that period, not suspected.

Baudelocque's multitude of positions of the head were markedly reduced in Bard's text. He discusses occiput posterior, face, and, oddly enough, combination of hand and head as the most frequent sources of delay and difficulty. For the first he highly recommends normal rotation; for the second, a much longer trial of labor than usual before resorting to any type of operation; for the third, repeated attempts to replace the hand or arm. According to Bard's experience the vertex enters the pelvis in the majority of labors with the sagittal suture in the transverse diameter.

"Preternatural labours" is the term Bard applied to all instances in which the body of the child was delivered before the head by art, or any footling, knee, or breech presentation, as well as "cross lies." Interference he regards as but infrequently required for the breech, except for the delivery of the head. For this he preferred the technique of Mauriceau and Smellie. Although he suggests that an assistant make pressure on the perineum to prevent laceration, he omits any mention of the more helpful fundal pressure.

A cross lie, or transverse, with dilated or dilatable internal os, should be corrected by turning before or quickly after the membranes ruptured; for the neglected case with impacted shoulder Bard felt that propriety lay in scissors and crotchet.

The continuing favorable reception of his book by the profession and students led Bard to include a chapter on the use of instruments, forceps, in his third edition. Of more than passing interest was Bard's admission that he had not, in the introduction to the first edition, mentioned Smellie among its authors whose works he had consulted. This was apparently due to the fact that he mistakenly felt Smellie was responsible for the widespread and possibly excessive use of forceps in England. However, Smellie wrote on the use of forceps in the introduction to his second edition (1754), "If these expedients are used prematurely, when the nature of the case does not absolutely require such assistance,

the mischief that may ensue will over-balance the service for which they were intended, and this consideration is one of my principal motives for publishing this second volume."

"The appropriate time to use the forceps," writes Bard, "follows no fixed rule; experience alone can enable us to deliver with satisfaction to ourselves, or safety to our patients." Bard's requisites for, and his described technique of, forceps delivery follow closely the rules laid down by Smellie. He enjoins his readers as to a cephalic application, the avoidance of compression of the head, and that forceps not be used to rotate the head. His favorite model was the short-shanked instrument of Smellie.

Bard contracts the statistics from two London hospitals with those of the Maison d'Accouchements de Paris during a ten-year period. He found perforation was done once in every 514 deliveries in London, but only once in every 1,331 in the service of Madame Bovain. He infers that earlier interference in London had precipitated the higher incidence of the use of the scissors and crochet. The use of these instruments, he writes, should only follow a serious and solemn consultation, particularly if the child is living.

Bard was a convinced subscriber to induction of premature labor, first suggested by Macauley, in pregnancies subsequent to a destructive operative delivery. He regards the choice of caesarean section a sad alternative in an obstructed labor, and the poor results in the use of section as due to its use only as a last resort after the woman was so fully exhausted that the outcome was necessarily fatal. Symphysiectomy he condemns as cruel and ineffective, in that the enlargement of the pelvis which might be obtained would not compensate for the pain and danger to both mother and child which attend it.

Bard had his patients use the recently rediscovered early ambulation in the puerperium. He advised "that after one or two days following child birth women should rise from their beds, and sit up for a longer or shorter time every day, according to their strength and inclinations . . . such changes of situation will promote the natural discharges."

Puerperal fever was regarded by Bard, on the basis of symptomatology and autopsy findings, as a peritonitis. His treatment was reliance on early bleeding, fomentations to the abdomen, and an acescent diet. He was so fortunate as never to have seen this disease in epidemic form during his years of practice. From 1809 to 1825 only six deaths from puerperal sepsis occurred in the New York Lying-In Asylum, then housed in the New York Hospital.[7] Although Bard points out the divided and contradictory opinions then held as to the cause, it is puzzling why he did not subscribe to the logical and already published ideas of Charles White and Alexander Gordon, both of whom he held in high esteem. Yet, a generation later, the evident truth of the subject was still disputed in high circles.

The final section of all editions is devoted to a discussion of the more common diseases of the newly born child. As to resuscitatory measures, he stresses avoidance of rough handling or sudden motion. "Let the infant," he writes, "be laid in an easy posture, clear the mouth and throat of any mucus that may

clog them, gently rub the back, and among all these means remember that external warmth is perhaps the most essential.'' Rooming-in was universally practiced by Bard's patients.

The purpose of this review has been to present a picture of Dr. Bard's general principles and practices only, and not to anatomize the successive editions in detail. Similarly the quoted passages have not been located as to edition and page, and some material drawn from his text has been paraphrased for conciseness.

In expressing a final opinion of the work one must recall that it was originally offered to improve the practice of midwives. In that respect I feel the book must have fulfilled its avowed purpose. From the third edition on, the text is intended for physicians. The subtitle is no longer to ''Correct the Errors and Improve the Practice of Midwives,'' but an ''Introduction to the Study and Practice of the Subject by Physicians and Medical Students.'' The language is technical, the discussion of complications and operative procedures well ordered and conservative in tone, and, as of the early part of the nineteenth century, fully abreast of the times. The book size changed in the third edition to octavo; the pagination expanded from 212 in the first, to 419 in the fifth edition. The illustrative case reports, carefully selected from the current literature, Smellie's, Perfect's, and Denman's collections, had increased from four in the first edition to one hundred and fifty-two (152) in the fifth, and serve well to explain the principles laid down, and to demonstrate the most successful practices.

Hugh Lenox Hodge[8] wrote, ''To Dr. Bard belongs the credit of being the first one to instruct upon a large scale the physicians of our country in the art of midwifery.''

I agree with Dr. Hodge, but go further to state that Bard's medium of instruction was a lucid and stimulating presentation of obstetrics, a real heritage of our early Federal days. Balancing a just moderation of praising the work and a necessary impartiality in touching its defects, I can in sincerity close this discussion with those famous last words of many book reviews, ''This work is well recommended to your attention.''

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POSSIBLE MECHANISMS OF SOME CONGENITAL DEFECTS*

C. C. CHAPPLE, M.D., PHILADELPHIA, PA.

THE study of developmental defects is the study of disease and drug action in general. The mechanisms by which defects are produced can be separated clearly here from the agents which induce them. Nowhere else can the activating agent be so definitely distinguished from the physiologic action it has started in motion.

Remarkably little is known about disease and drug action in either the unborn or the born. In spite of this, it is assumed that each is different and unlike every other.

The amniotic enclosure around the embryo is considered unique in its way, too, although its membrane is constituted along the same lines, and of similar materials, as other membranes. This one, however, is thought to be unresponsive to influences which change the others. We have taken a "foreign-body" attitude toward the amniotic sac and its contents, overlooking its human origin and environment. Perhaps it might be to advantage to approach the problem from more of a "one-world" angle.

In considering each member of each category something unique and in searching for the differences which might emphasize dissimilarities, fact has been piled upon fact. Nearly all the information we have at hand has been uncovered this way. The importance of the "difference" would seem to acknowledge that a similarity must exist somewhere and that there may be a danger of its being thought to be greater than it really is. However that may be, it cannot alter the facts themselves to regard them from another point of view here, in this discussion which might be called "A Search for Common Ground."

As far as the agents suspected (or proved) of inducing developmental defects are concerned, this common ground is not conspicious among them. We know them outside in infinite detail. Viruses, rickettsial bodies, bacteria, lead, mercury, dyes, and nitrogen mustard have conspicuous differences. Radiations, emotional shocks, and electric storms do not resemble any of them, nor each other, very closely. Each of this strangely assorted lot is suspect in developmental defects and so they have this much in common from the start. This may seem a long reach for support and seem more philosophic than physiologic, so let us conduct the search inside, and examine the neuro-hormonal mechanism which each, or all, might employ.

The "sex" hormones with which you deal so much in obstetrics and gynecology are pretty basic elements in the biologic sense. Of them estrogen alone is really stable and durable. It has the simplest chemical structure. Androgen and progesterone are only slightly more complex (and in that order) but their stability is nil compared to that of estrogen.

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These "sex" hormones are present in both sexes and apparently in everything that has ever been alive. Estrogen, to which the others may revert, is found even in the ancient remains of unicellular life. Chalk, basically a calcium structure, has estrogen activity, as have crude oil, asphalt, pollen, seeds, coal and the coal tar products, etc. They have been demonstrated to be there by such men as Aschheim and Zondek in your field. One of the most thorough of them, Zondek, preceded me in this guest lectureship before your Society.

Besides appearing to exist in every cell, these hormones have been noted as affecting every physiologic process in which they have been studied. In a search of medical literature some years ago we found published observations on 113 physiologic functions influenced by estrogen and 63 by progesterone, exclusive of those considered to have to do in any way with primary or secondary reproductive organs. Among them the hormones were shown to influence absorption, cell division, and mental altitude. Is reproduction only "sex," or are absorption of food and oxygen, cell division and growth as essential as the genitals themselves? And what about the mental attitude?

These universal hormones are sex hormones as they are body or mind hormones and they emphasize the indissolubility of sex, psyche, and soma.

In the higher animals and man, at the other end of the hormone scale are the pituitary hormones. These are on the level of a commander, a colonel perhaps, and the "sex" hormones are the sergeants who see that the job is done and report back to headquarters. The pituitary is given enormous credit. This tiny gland is said to have 26 separate functions. Each, however, is simply to alert a manufacturing gland below it into large-scale production of the hormone required or to desist. These hormones must vary largely in their attractiveness to the manufacturers since, on the face of it, it would seem extravagant to have such versatility in other respects than election of site, being delivered to cells in which versatility does not exist at all. Each cell, wherever it may be, can only expand or contract (which it does normally in a rhythmic alternation) and in doing so continue or discontinue, at the word from the hormone, whatever each accomplishes in that phase.

The pituitary is strategically situated. All nerve impulses must pass through it to and from the spinal cord. These and other nerve impulses are obviously electrical. Hormones are no less so, as atoms in general are electromagnetic equilibria, but we forget this since we measure them by a different discipline—this time chemistry. This is of no great moment except that the close relationship in the pituitary suggests that the hormonal fraction of the neuro-hormonal mechanism may be just over the edge into chemistry.

It seems reasonable to me, and important, that, since we can detect chemically or by bio-assay a number of remarkably effective substances in the pituitary, we seem to be mistakenly attributing powers to this gland which properly should be given to that part which we usually consider the province of the psychiatrist, the seat of rage and fear, and in terms of epilepsy and tumors. The pituitary might be a major communication center. But can it

really evaluate the circumstances, and, deciding that anger should be the thing, order out the adrenaline? Is it the pituitary that recognizes and responds to the attractiveness of some member of the opposite sex? I would prefer to think it was the brain.

All the foregoing is relevant because the normal pituitary hormone ACTH needs only to be increased in amount in a normal animal to cause her to be sterile, miscarry, have premature offspring, or to induce in her progeny any of the developmental defects seen in the human. The time of the raising of her ACTH level and its degree determine the result. (The difference between raising and rising is the difference between the objective and the subjective, or the laboratory experiment and, perhaps, the mother of the patient.) ACTH does not of course accomplish this result alone. It stimulates larger scale production on a more somatic level. The most readily recognizable response to this hormone is in the adrenal but there is reason to believe that it is in no way limited to that gland's output since no circulating hormone appears to be alterable without changing all the others. They are as closely interrelated as though they were meshed together like gears and each seems to act as well in reverse as in forward, or to have as strong an efferent action as an afferent response. Any single one observed as the potent factor in any physiologic phenomenon must not be considered as acting exclusively on a studied tissue at any particular site, or as the only one which is acting on it. The possibility that the observed hormone itself can be altered by a higher power, which may be changing both the hormone's level and the physiologic response together, must be considered. Estrogen induces deposition of bone, progesterone stimulates cell division or growth of it. Androgen and thyroid mature the epiphyses. Adrenaline will cure rickets. All of these affect blood calcium. Yet because someone was focused on the parathyroids, and these glands are surgically accessible, they are held responsible for bone formation and disturbances in general associated with calcium change. This is one of many examples. It is mentioned now to illustrate the point and to show that cause-and-effect relationships are not always what they appear to be.

The interdependence and interrelationships of all parts of the body are so close that no part can be changed without changing all the rest. Any change in a cell must change the blood and any change there must be reflected upon every cell since it would be delivered in its changed state to each of them.

Hormones in the blood affect many processes besides the conspicuous one. For example, hormones, both high and low on the somatic scale, affect secretions. They influence the rate of their production, pH, and salinity, among other things. Observations here have again been made on various hormones. The sex hormones have been the most completely studied in these particulars. Which hormone may be the instrumental one is not important but it is important to realize that changes like these are made in response to word from the pituitary, or, perhaps, the brain.

Minute changes in the salinity or pH of the medium around the egg of an aquatic animal will induce gross monsters or will be lethal to the developing

organism. Is it not possible that the human ovum is equally responsive to changes in its medium? Then, is it not logical that an emotional state, an infection, or some other agent might induce the brain to increase the hormone which includes, at least collaterally, these among its other responsibilities? Adrenaline is known to rise under "stress" conditions. Since it is a foe of estrogen, an increase in adrenaline must change those things which have been assigned as responsibilities to estrogen. (Are they? Does it matter?) Among these is salinity of secretion.

Fluid transfer is another function under the wing of the pituitary—and others. Pituitary gonadotropin and the "female sex" hormones, again among others, have been shown to influence the permeability of the intercellular cement substance. The facility of access to and from the cell depends largely on the state of this cement. Lurie, of the Henry Phipps Institute, found he could make it soft or leathery by progesterone or estrogen, respectively. By administration of these hormones, the membranes of the lungs of his animals were made penetrable by particles as large as tubercle bacilli or impervious to them. Permeability of membranes in general is not highly selective.

Permeability and fluid transfer may also be essential mechanisms in the production of developmental defects. The possibilities would start with the penetration of the ovum. The sperm, too, has this ability to soften hyaluronic acid, the critical substance in the intercellular cement. Using it, sperms thin the uterine secretion and reach the ovum, which one of their number enters. This is fertilization. Conception is implantation. Many an egg may be fertilized only to be lethally changed by the secretion while en route to the uterus and as a result may not become implanted. This has been reported as being the case in animals by Corner of the Carnegie Institution and it seems reasonable that infertility, especially that under conditions of stress, might be accounted for in this way. The other sperms in the high count required for conception may soften the uterine mucosa for the implantation of the ovum, which now, presumably, would be bearing the contained sperm's penetrating ability. Besides these factors for implantation, the mother, after ovulation, would be expected to have easily penetrable intercellular cement substance from her progesterone. These factors may help to explain why an unfertilized egg seems never to be implanted while a fertilized one may or may not become so.

After implantation, for about two months, the embryo develops and then grows and matures as a fetus. At term the original ovum has become about 10 billion cells. This prodigious number is reached by about 40 cell divisions, or approximately the number of weeks of gestation. The unborn does not develop quite by geometric progression, of course, but the curve of his increase is distinctly exponential, slow at first and extremely fast during his final trimester. The amniotic fluid on the other hand does not form on a corresponding curve. It is proportionally very much more at first and having reached its maximum at mid-gestation, 1,800 c.c., average, falls to about 800 c.c. at term. The absolute quantities are not so interesting, however, as the relative amounts compared to the volume of the unborn.

Until the embryo is approximately 6 weeks of age his conformation from his head to his tail is nearly circular. Then, though, his head begins to rise from the cephalic flexion in which he has carried it. It is important that there be room enough around him so that he can lift his head from his chest. Under normal circumstances, of course, he is free to do so since the amniotic fluid surrounding him is eightfold, or more, his own volume. In it, with only buds of arms and legs, he can move freely. Its absolute volume, though, is small, and a difference of 2 c.c. or so in it is the difference between freedom of movement and the confinement of his head in the embryonic position.

The amniotic sac which encloses the fluid is another membrane tied together with the same intercellular cement. There seems little reason to suppose that it is unresponsive to the influence of the blood which surrounds it, nourishes it, and to the hormones the blood contains. This should be the case whether the sac originated from the implanted ovum or from the mother. Additionally, there is reason to believe that transfer of fluid through the amniotic sac is possible. Oligo- and polyhydramnios tell us only of the state of affairs at term or at the time observed. They supply no evidence that whichever is present has been there from the start. The evidence of fluid transfer through the amniotic sac is direct and also lies in the study of such developmental defects as the short mandible and cleft palate so frequently found in association, and which among other names is called Andy Gumpism.

In the early life of the embryo, while his head is still on his chest, the tongue lies between the sides of the palatal arch. His head must be lifted from his chest to allow the tongue to fall down into the mouth so that these sides are free to unite into an arch. If it is not raised, the already intact tongue prevents their union and the tongue grows into the nasopharynx. There seems little doubt of the origin of this defect for several reasons: The structures involved arise from different anlagen, from different layers at different times. A gene covering this odd assortment has no parallel. The structures are in no other way related, to our knowledge, but by their mechanical relationship where the one can so readily affect the other. This combination of defects appears with enough regularity in animal experimentation that it is used as the index for occurrence rate of defects. Defects associated with it are those of pressure: posteriorly displaced and flattened larynx; angulation of the manubrium on the body of the sternum; indentation of the chest under the angles of the mandible; pressure hypoplasia of the mucous membrane of the jaws at points of contact, and flattening of the back of the head. It has been induced experimentally with every effective agent. Finally, an increase in the level of various circulating hormones produces it, in the absence of any other factor.

The fact that it is also found on a hereditary pattern makes it worth while to comment for a moment on inheritance. Heredity is neither an agent nor a mechanism. It is a means by which damage to an antecedent can be transmitted to his posterity. (Presumably benefits can be transmitted as readily but we prefer to think in terms of deficits, deficiencies, and damage.)

But in the miniscule effigy we seem to think exists in every germ cell of every person, we cannot tell that processes or patterns are not inherited. It seems quite probable that they are. Certainly, anatomically specific genes would be expected, if damaged, to produce a skinless arm or an armless skin, the vessels of an otherwise absent part, or something of this nature. But these do not happen. Maybe the inheritance in Andy Gumpism is a hormone pattern, or a susceptibility of the mothers to emotional or other agents' stimulation of the hormones.

Among the agents which induce this defect are some which can be watched in the laboratory and seen not to enter the amnion nor the embryo. Dyes, for example, and nitrogen mustard induce it and neither crosses the placental barrier. This, in a positive way, is important. Even more important is the generally unrecognized fact that not a single agent which induces this, or any other developmental defect, has ever been shown to enter the amniotic sac or the embryo. This is true of poisons and infections as well as other less demonstrable agents. It seems remarkable that the direct-attack-on-the-embryo theory has persisted to the exclusion of all others in the face of this.

Later, in the fetus, organisms of various types have been cultured and have been shown beyond doubt to have entered the amnion. Some of these are destructive to the fetus but most cause in him the disease of his mother. None of these, however, seem to enter in the first trimester nor to damage the development of the embryo.

The diseases which may induce developmental defects comprise quite a long list. All of those on it have not been proved to do so. The list starts of course with German measles which is on pretty solid ground as a potential damager of early development, though fortunately each individual's odds are good against it. Measles and typhoid were once labeled "great aborters" and as such seldom left residual damage. Infectious mononucleosis, dengue, sand-fly fever, malaria, typhus, influenza, and still others are among those suspected.

Is there common ground to be found among them? It is definitely not in the size of their organisms which range from undiscovered virus to protozoa. But are they similar in any way in the body?

These diseases induce the same blood picture, i.e., a leukopenia with a relative lymphocytosis. This is what is known, incongruously, as the virus blood picture, although most of the viruses associated with it have yet to be discovered, and most of those already demonstrated do not induce it as regularly as some organisms of other sizes. In contrast to that blood picture, the diseases which invade the fetus later have a high poly count, scarlet fever, pneumonia, meningitis, chicken pox, etc.

May I remind you that nothing circulating in a blood vessel originates within it. Every type of cell is made elsewhere, at a myriad of sites, as is every other component of blood. Each must enter the blood stream through an in-

tact membrane and, at its particular destination, leave it again through another. A "blood picture" is a picture of collaboration between the manufacturers all over the body, and the permeability of the blood vessel walls. Nothing so extensive could be expected to be accomplished except through central control. This seems reasonable enough.

It is clear that there are no sharp division, no complete distinction, and no absolute line of separation existing anywhere in medicine. There is no thought that an exception exists here. It is only that the trend seems worth calling to your attention.

The diseases with leukopenia and relative lymphocytoses are those which may be complicated by encephalitis and which have regularly a psyche which is disturbed out of all proportion. This encephalitis has no infiltration of cells and if prolonged to the point of death may show a demyelinization but nothing more. The disturbed psyche is conspicuous in typhoid and typhus but even in measles and German measles the wretchedness accompanying the disease far exceeds that expected from the observable signs. Mumps and whooping cough with their absolute lymphocytoses are the exceptions. They may also have encephalitis but the probability and the severity both are less than can be the case with any of those which may induce developmental defects.

These diseases with the leukopenia and relative lymphocytoses are those to which "transfer of maternal immunity" takes place whether or not the mother ever has had the disease. Infants are routinely immune to them all, while, incidentally, they are highly susceptible to any with a high poly count.

It might be worth observing here that susceptibilities in general seem strangely related to blood pictures. The infant, who already has a high percentage of lymphocytes, is relatively immune to those diseases which have that blood picture. The adult with his predomination of polys is again relatively immune to diseases with high poly blood count.

These leukopenic diseases are those to which permanent immunity is difficult to achieve. The temporary immunity from typhoid inoculations is notorious as is the dearth of permanently protective measures against any disease with this blood picture. Roseola, measles, and German measles are ill defined as to causative organism and are distinguishable clinically only when they fit classical patterns of severity and duration, and, like German measles in particular, are very likely to occur more than once. The highest incidence of this disease is in the 20 to 30 age group, as is the occurrence of the severe measles, typhoid, and malaria. "Subclinical" infections have by this age practically wiped out the high poly diseases but, curiously, this totally unprovable conception of a phenomenon seems not to apply to the lymphocytotic diseases.

These leukopenic diseases cause exacerbations of allergic symptoms which are quelled by the high poly group. They are the diseases which benefit nephrotic patients, when they can be acquired, while the high poly diseases

are disastrous to patients with this condition. Gamma globulin can be used with some assurance in diseases with the leukopenic blood picture and is useless against any aspect of any disease with a high poly count.

There are other points, too, of similarity among them. They are diseases of increased permeability and of general invasion. Patients with any of them have an involvement of lymph tissue or glands somewhere. It is generalized in measles, postauricular in German measles, in the Peyer's patches in typhoid, for example. All may have skin manifestations of the same general nature, all may have chest involvement resembling miliary tuberculosis—which itself has this blood picture. Under the usual epidemic conditions the specific differences mark each disease. Under pandemic conditions they may be indistinguishable.

Now, after it has been pointed out where common ground seems to exist in a general way among the diseases which may induce developmental defects, it should be added that every other agent which can induce developmental defects is one which also tends to induce this blood picture.

One can only conclude that some common ground may exist.

The remainder of this presentation is short and should be obvious by this time.

By mid-gestation the fetus has long legs and arms and only once or twice his own volume of space in which to extend them. He can rest his back along an encompassing wall and push his feet against the opposite side. When he's getting crowded enough to do this hard, his mother "feels life."

After that he grows much larger and the amniotic space around him, instead of increasing with him, diminishes in volume. The sphere, which was once the shape of the amnion, becomes distended by fetal protuberance. The uterus attempts to regain that shape and its Braxton Hicks contractions make him as spheroid as possible. He adjusts resignedly, unable to push this vigorous muscle away without using his whole back to do it. He shortly finds himself compressed into a posture which he maintains for the rest of gestation. Dislocations and distortions may result but he is comfortable. Later when he is finally born, he still prefers that posture, his "position of comfort." An examiner assisting him back into it, in the absence of the supportive uterine wall which held him there, demonstrates that few babies indeed had the conventional posture of straight anterior flexion in utero. This "folding" technique can account for a great variety of anatomic "anomalies." Most of these are skeletal and obvious. Some are weaknesses and paralysis due to pressure on a nerve or its blood supply. Some are vascular where the circulation was established to a twisted extremity and became itself twisted when the extremity straightened out after birth. Their variety is infinite and most, fortunately, of insignificant importance beyond the interest of the physician and the mother in their explanation.

A few, formed in early embryonic times when a little pressure or restriction of movement caused extensive damage, are serious. They occurred on

presenting surfaces and parts which at that time were the lower lumbars, the mid-cervicals, and the top of the head. These are the sites of meningoceles, bifidas, and, earlier and tighter still, the rachischises.

The list is not complete here but it is hoped that it is long enough to illustrate. The discussion must be brought to a conclusion. It might be summarized by saying that, in the search for common ground, agents, of which many are recognized, can be separated from mechanisms, of which few indeed are established; and that this search seems to make it clear that it is the brain which is affected primarily by all the agents and which, in response to their stimulation, moderates the entire body in a continuance of a normal process beyond its normal discontinuation time, and that this is accomplished through existent controls and normal channels.

ON THE ORIGIN AND DEVELOPMENT OF UTERINE FIBROIDS*†

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JUST when uterine "fibroids" were first recognized and described we do not know, but it is probably safe to assume that their association with the human race dates back to earliest antiquity. While there has been no dearth of published articles dealing with the diagnosis and management of these common tumors, one is left with the impression that curiosity regarding their origin and development has been confined largely to meditation, since there are comparatively few reports devoted to this aspect of this singular ailment. Perhaps the fact that fibroids are strictly feminine and most physicians are men partly explains this apparent indifference. Then, too, fibroids are rather friendly tumors. They are almost always benign, they grow slowly, and do not necessarily cause distress. When viewed in another light, however, the picture is not nearly so innocuous. It has been estimated that one out of every four or five women over 35 years of age has a uterine fibroid.[1] This does not mean that 20 per cent to 25 per cent of women have symptom-producing tumors. Yet trouble from this source is common, for approximately 60 per cent of all laparotomies performed upon women for pelvic disease are due to fibroids.[1] Something less than 1 per cent of fibroids undergo sarcomatous change. For these and for other reasons, if, indeed, an excuse is necessary, it appears justifiable to dust off the question as to why uterine fibroids occur and grow.

While long usage of the word "fibroid" has firmly established this term in medical parlance, histologically, human uterine fibroids are composed chiefly of involuntary muscle similar to that constituting the myometrium. Although connective tissue is also present to a greater or lesser degree, the bulk of most of these tumors is made up of involuntary muscle. The term fibroid is here used in its popular sense as referring to all types of uterine myomas.

Our interest in this problem of origin and development goes back a long time but it is only in the last four years that we have attempted to do something about it.[2] That there appears to exist some tie-up between ovarian function and uterine fibroids has long been recognized. These tumors thrive during the years of greatest ovarian activity and their involution follows ovarian regression. This ovary-fibroid relationship has become widely accepted as an estrogen stimulation-tumor growth affair. Witherspoon[3] explained the frequent occurrence of fibroids in the uteri of Negro women on the basis of long-sustained elevated estrogen levels due to cystic change in the ovaries secondary to pelvic inflammatory disease. He reported a series of

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cases where this cause-and-effect relationship appeared to exist. Nelson[4] and Lipschutz[5] have demonstrated that it is possible to induce formation of fibromas in castrated guinea pigs by the prolonged administration (implantation) of estrogen. When progesterone, testosterone, or desoxycorticosterone was present or added, no induced tumors occurred. Lipschutz[6] spoke of this as the antitumorigenic or antiestrogenic effect of these steroids. Despite the facts that these tumors induced in the castrated guinea pig were true fibromas —not myomas, and did not occur in the guinea pig's uterus—the studies may nonetheless be of considerable significance. Though for the present applicable largely to the guinea pig, this basic interrelationship between the growth of benign tumors and estrogenic hormones may one day find its proper place in the human fibroid jigsaw puzzle. Similarly, the antitumorigenic effect of other steroids may serve as a useful clue to the practical control of fibroid growth. Goodman[7] reported on his efforts in this connection in 1946. While there can be no denying the existence of some relationship between the growth of uterine fibroids and the production of estrogen by the human ovary, the details of this interrelationship are by no means complete.

In accepting some sort of growth-stimulating relationship between estrogen and uterine fibroids we are faced with the necessity of also attempting to understand why the uterus (myometrium) itself does not undergo increasing enlargement in the presence of estrogen sufficient presumably to bring about progressive growth of large fibroids. In our experience, it has been difficult to cause detectable increase in the size of the human uterus by the administration of estrogen alone. The endometrium may be forced into a state of marked overgrowth but extensive hyperplasia and/or hypertrophy of human uterine musculature resulting in a significantly enlarged uterus is uncommon in our experience. The uteri of laboratory animals can be made to enlarge by the prolonged administration of estrogen but, even here, much of this increase in size is due to the tremendous overgrowth of the contained endometrium. In 1951 Otto Schwarz[8] reported on uterine enlargement. At that time he confirmed the work of Fletcher Shaw who had described three types of enlargement of the nonpregnant uterus. Both Shaw and Schwarz found uterine hypertrophy to be the least common cause of diffuse uterine enlargement, constituting approximately 5 per cent of all cases. When we consider the relative infrequency of any type of diffuse uterine enlargement in the absence of pregnancy, and more specifically the rarity of true uterine hypertrophy, then it becomes difficult to accept estrogen stimulation as the *only* factor underlying the growth of uterine fibroids. If estrogen were the only factor, then one might expect that prolonged elevation sufficient to bring about the development of a fibroid would also reveal uterine participation in the form of myometrial hypertrophy. This, however, does not occur.

It is of some interest to mention here the study of Randall and Odell[9] dealing with the behavior of fibroids in pregnant uteri. Estrogen levels are normally elevated during gestation, yet these observers found little evidence that fibroids present in the wall of the gravid uterus actually *grew* during pregnancy.

Heredity has commonly been called upon to explain the greater frequency of uterine fibroids in the Negro race. It has also served to explain the occurrence of fibroids in sisters, even twin sisters. Perhaps the predisposition is inherited, as appears to be true for other diseases and neoplasms. Heredity of itself, however, probably does not account for the presence of these tumors. Indeed, some deny that heredity is an important factor at all. Matas[10] studied this aspect of the problem and pointed out that medical missionaries found a low incidence of uterine fibroids in the pure African Negro and that presumably the higher incidence among American Negro women could not be attributed entirely to heredity.

The relationship between uterine fibroids and infertility is by no means clear. Women with fibroids do become pregnant. Yet the fact that some do not offers an avenue for intriguing speculation. Can it be that anovulatory menstruation is much more common among women who develop fibroids, and that infrequent ovulation accounts for both lowered fertility and an elevated estrogen level favoring growth of fibroids? This possibility deserves study.

Regardless of what may appear to be a reasonable but still hypothetical explanation for the *growth* of these tumors, we must still explain why some women develop them and others do not. What is the origin or anlage for such tumors? This question has troubled the minds of others and has not as yet been satisfactorily answered. Both Robert Meyer[11] and DeSnoo[12] tentatively answered this question by presupposing that there existed small cell nests which, under appropriate stimulation, presumably by estrogen, would develop into full-grown fibroids. Both claimed that the presence of these cell nests, which DeSnoo called "genitoblasts," could develop into either a fibroid or into an adenomyoma, under appropriate stimulation. Meyer considered these nests to be made up of immature muscle cells measuring 0.02 to 0.20 mm. in diameter. The hypothesis presupposing special cell nests is not only intriguing but indeed almost a necessity in order to explain the many aspects of fibroid-tumor behavior, such as their presence in some and absence in others, the low incidence of recurrence following adequate myomectomy, etc.

In the present state of our knowledge, the human animal does not appear to be the most suitable medium for a controlled study on the development and growth of myomas. Furthermore, since these tumors rarily arise spontaneously in animals and their induction by experimental means even in the guinea pig's uterus is impossible, the animal approach does not appear to be feasible. It is for these reasons that we have attempted to explore the problem by tissue-culture techniques. Believing that, once we succeeded in overcoming the problems related to satisfactory culture and identification of the myoma cells, we might then undertake other studies dealing with growth stimulation and growth restraint, we embarked upon this tissue-culture study four years ago and our first report in 1953 dealt briefly with preliminary aspects of our work. During the intervening years we have endeavored to gain a better understanding of these tumors. The present report deals with the development of improved tissue-culture techniques more suitable for the

cultivation of adult human tissues and also with the complex task of cell identification. The latter problem has turned out to be more difficult than we had at first anticipated. In an attempt to clarify the question as to whether the outgrowths from tumor explants originate from the smooth muscle or from the connective-tissue components of myoma tissue, we have incorporated in the present experiments the cultivation of adult human fascia from each of 20 patients with fibroids to serve as control fibroblastic tissue to be observed along with the growth from myoma and myometrial specimens.

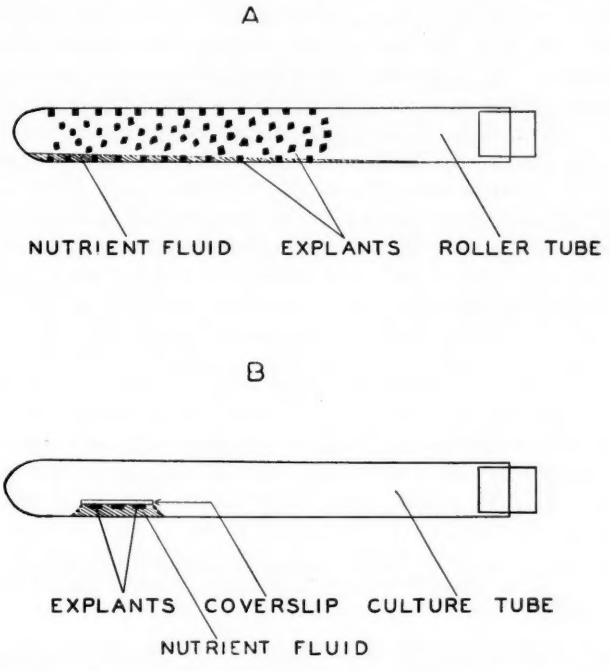

Fig. 1.—*A*, Primary roller-tube culture. *B*, Horizontal cover-slip-tube culture.

Materials and Methods

Specimens of myoma, myometrium, and rectus fascia were obtained from the same individuals at the time of hysterectomy. Multiple small fragments approximately 1 c.mm. in size were cut from each tissue and suspended in individual depression slides containing cord serum as the transferral fluid. Our primary cultivation technique was a modification of the original roller-tube method of Gey.[13] It was specially designed to facilitate the cultivation of slow-growing adult human tissues. Forty to 50 explants were placed directly on the inside glass surface of a test tube by means of a bent-tipped capillary pipette (Fig. 1, *A*). After 10 minutes the transferral fluid which has meanwhile drained to the bottom of the tube was removed and exactly 0.3 ml. of nutrient fluid was added. The composition of this nutrient material was 4 per cent chick embryo extract, 56 per cent Hanks[14] balanced salt solution, and 40 per cent human cord serum. Penicillin and streptomycin were also incorporated to make a final concentration of 100 units and 0.1 mg. per milliliter, respectively. The tubes were stoppered and incubated at 37° C. in an almost horizontal position in an ordinary roller-drum apparatus designed to complete

12 revolutions per hour. The fluid medium was changed every third day unless more frequent renewals were indicated by decreases in pH.

Generally at between 14 to 30 days of cultivation most fragments produced an extensive proliferation of cells. In subculturing, the original explants were easily freed from their extensive outgrowths and individually moved to a clear area near the lip of the tube. Employing a curved-tip pipette and a small volume of transferral fluid, the explants were transferred to a depression slide. They were then transplanted to secondary roller tubes or to horizontal cover-slip tubes. In the preparation of horizontal cover-slip-tube cultures, a minute drop of chick plasma was streaked on the surface of an 11 by 22 mm. No. 1 cover glass which had previously been inserted in an ordinary test tube. Three to 6 explants were then deposited on the cover slip and the transferral fluid (cord serum) as well as the excess plasma was carefully removed from around the explants. In experiments where direct comparison studies were contemplated, explants of myometrium, fascia, and myoma were placed in a row on the same cover slip. The cover slips were turned over and fixed approximately 1 inch from the bottom of the tube by the placing of a minute drop of transferral fluid where the edges of the cover glass touch the tube. The unstoppered tubes were placed in a horizontal position for 30 minutes during which time the explants became firmly attached to the cover glass. Exactly 0.4 ml. of nutrient fluid was added to each tube; the cultures were stoppered and then incubated in a horizontal position at 37° C. in flat wire trays. The nutrient fluid becomes trapped between the cover slip and tube. In this manner the explants were in a hanging-drop-like position and constantly in contact with the fluid medium (Fig. 1, *B*). Usually an extensive outgrowth in this type of culture occurs within 48 to 60 hours. We have maintained such cover-slip cultures as long as 60 days without destructive changes in the cellular outgrowth. In such instances the nutrient fluid is changed every third day. Generally, the entire cover slip is covered with proliferating cells after approximately 30 days. At the termination of the desired growth period, the cover-slip cultures may be fixed and differentially stained for histological study or prepared in a simple microscope-slide perfusion chamber for living phase-contrast studies.

We have designed a simple microscope-slide perfusion chamber (Fig. 2) which has been found exceedingly useful in studies on the effect of contractile and oxytocic agents on proliferating cell types. The agents were dissolved in the proper solvent and added to the inlet tube. Then, by placing a piece of porous filter paper at the outlet tube exit, the solution was drawn through the chamber. Such perfusion chambers are simple to construct from readily available laboratory equipment and are ideally suited for recording typical observations by still and motion picture photomicrography. A phase-contrast microscope (American Optical) utilizing 8, 4, and 1.8 mm. (dark) objectives was used for the study of living preparations. Cinematographic records were made of typical findings, employing a time-lapse device (Matt) in conjunction with a Cine-Kodak 16 mm. camera at rates as slow as 1 frame per minute and as fast as 1 frame per second.

Original tissue specimens as well as whole mount cover-glass cultures were fixed in Bouin's fluid and subsequently differentially stained by Masson's trichrome technique.

Infrared spectrophotometry measurements were made on preparations from original tissue as well as cultured cells by means of a Perkin-Elmer, model 21, double-beam recording spectrophotometer. Original tissue specimens approximately 1 c.c. in size were quickly frozen in liquid nitrogen and pulverized to a fine powder in a mortar. The powder was washed with a small volume of acetone in order to accelerate air drying. It was then transferred

to a tissue grinder containing 1 ml. of distilled water and a fine suspension was prepared. This suspension was added drop by drop repeatedly on the surface of silver chloride sheets until a dry specimen of a thickness appropriate for spectral absorption was obtained. In the preparation of cultured-cell specimens, primary roller tubes in which all original explants had been removed were employed. Such primary tubes with cellular outgrowths coating the entire tube were fixed quickly by replacing the nutrient fluid with acetone. After 5 minutes the acetone was removed and the tubes were air dried. Finally, the cells were scraped from the sides of the tube, placed in a tissue grinder, and handled in exactly the same manner as described for original tissue preparations.

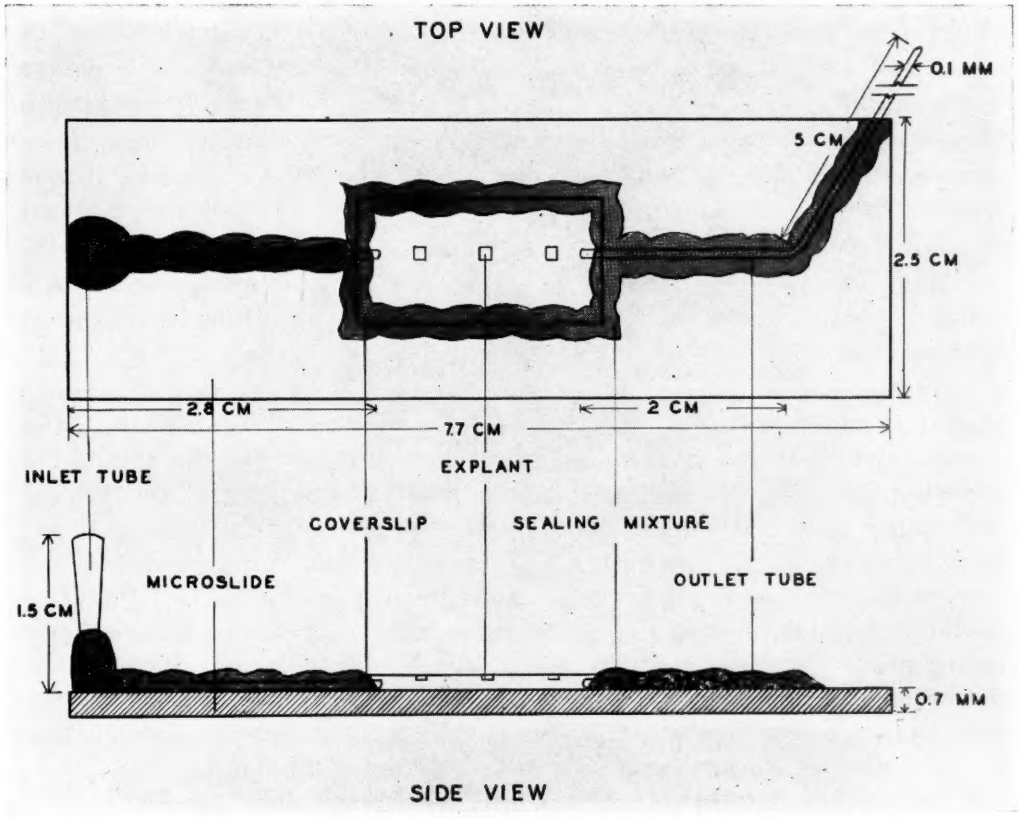

Fig. 2.—Diagram of a simple microscope-slide perfusion chamber.

Oxytocic and contractile drugs were prepared in stock solutions containing 0.1 mg. of agent per milliliter of distilled water and then diluted with Hanks balanced salt solution or our standard nutrient fluid with or without chick-embryo extract. The hydrogen ion concentration of the final solution was always adjusted to pH 7.4.

In later experiments, adenosine triphosphate* (ATP) at 0.05 M concentrations was prepared in the cold, pH adjusted to 7.00 and frozen. Prior to use, the solution was thawed and diluted, one part to nine parts special salt solution. This salt solution, consisting of 0.14 M KCl, 0.0014 M $MgCl_2$, and 0.0285 M $KHCO_3$, was isotonic for cultured cells.

*K_2H_2 ATP $4H_2O$, Pabst Laboratories.

Observations

Morphologic and Cytologic Appearances.—

The observations presented in this section were made on primary roller-tube cultures and on cover-slip preparations differentially stained by Masson's technique.

In their mode of outgrowth myometrial and myoma cells form an adherent reticulum with intercellular bridges connecting cells laterally with each other, whereas fibroblasts appear to grow in a rather haphazard manner, at times forming a loose reticulum but no intercellular bridges (Figs. 3, 5). *The major differentiating characteristic previously reported and further verified in these experiments was the presence of longitudinal or linear striations in the myometrial and myoma outgrowths as compared with their complete absence in fibroblastic cultures of human fascia.* This difference is clearly illustrated in Figs. 5 and 6 showing outgrowths from three different types of tissue grown adjacent to each other on the same cover slip. Longitudinal striations are considered to be the most important morphologic distinguishing feature of embryonic or adult smooth muscle.

Many European[15] and American[16] workers have noted similar striations in living and stained cultures of *embryonic* smooth muscle cultured in vitro and have used the term myofibrils to describe them.

Another differentiating characteristic is the greater number of granules present in fibroblastic cells, especially in older cultures. Apparently this increased granularity explains the affinity these cells have for the aniline blue dye when stained by Masson's trichrome method. The cytoplasm of myometrial and myoma cells, on the other hand, having few granules, generally takes on a more homogeneous red stain. This staining differential is not consistent, however, so it cannot be relied upon to identify unequivocally one cell type from another. As illustrated in Fig. 4, the outgrowths of muscle cells have a more homogeneous spindle shape than those found in fibroblastic cultures. Also, the fibroblasts consistently appear smaller in size than uterine cells. Myoma cells and, to a lesser extent, myometrial cells form a vacuolar maize pattern in older cultures which is never present in a culture of fibroblasts.

Proliferative outgrowths of muscle cells invariably retract after two to three weeks to form dotlike colonies throughout the tube. These fragments of new tissue produce cellular outgrowths in a reticular fashion similar to original explants. On the other hand, fibroblastic outgrowths do not retract but continue to proliferate as dense sheets of cells which generally coat the entire primary roller tube with a homogeneous layer of cells. After removal of all original explants, such fibroblastic sheets can be trypsinized, prepared as cell suspensions, and subcultured. In this manner we have isolated and established fibroblastic cell strains which can be maintained in continuous cultivation indefinitely. On the other hand, we have repeatedly been unsuccessful in our attempts to establish similar myometrial or myoma cell strains.

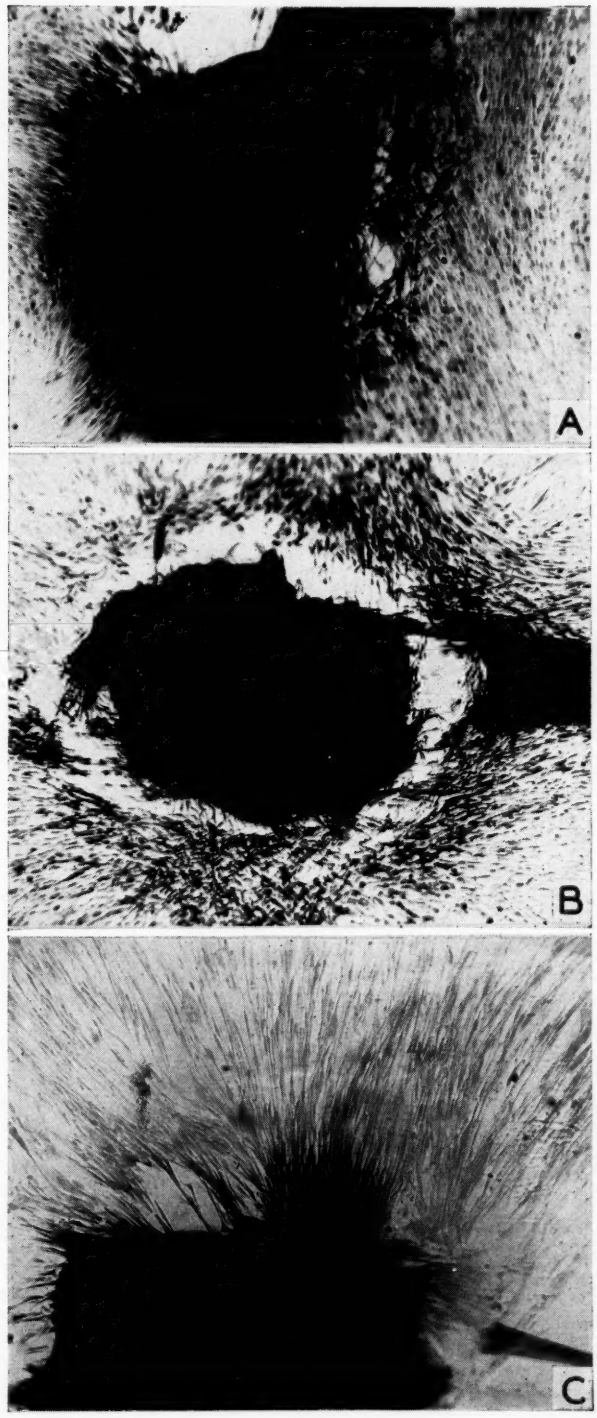

Fig. 3.—Characteristic outgrowth patterns of (*A*) myometrial, (*B*) fascial, and (*C*) myoma tissue cultivated on the same cover slip. (Bouin's fixative; Masson trichrome stain. ×53; reduced ⅙.)

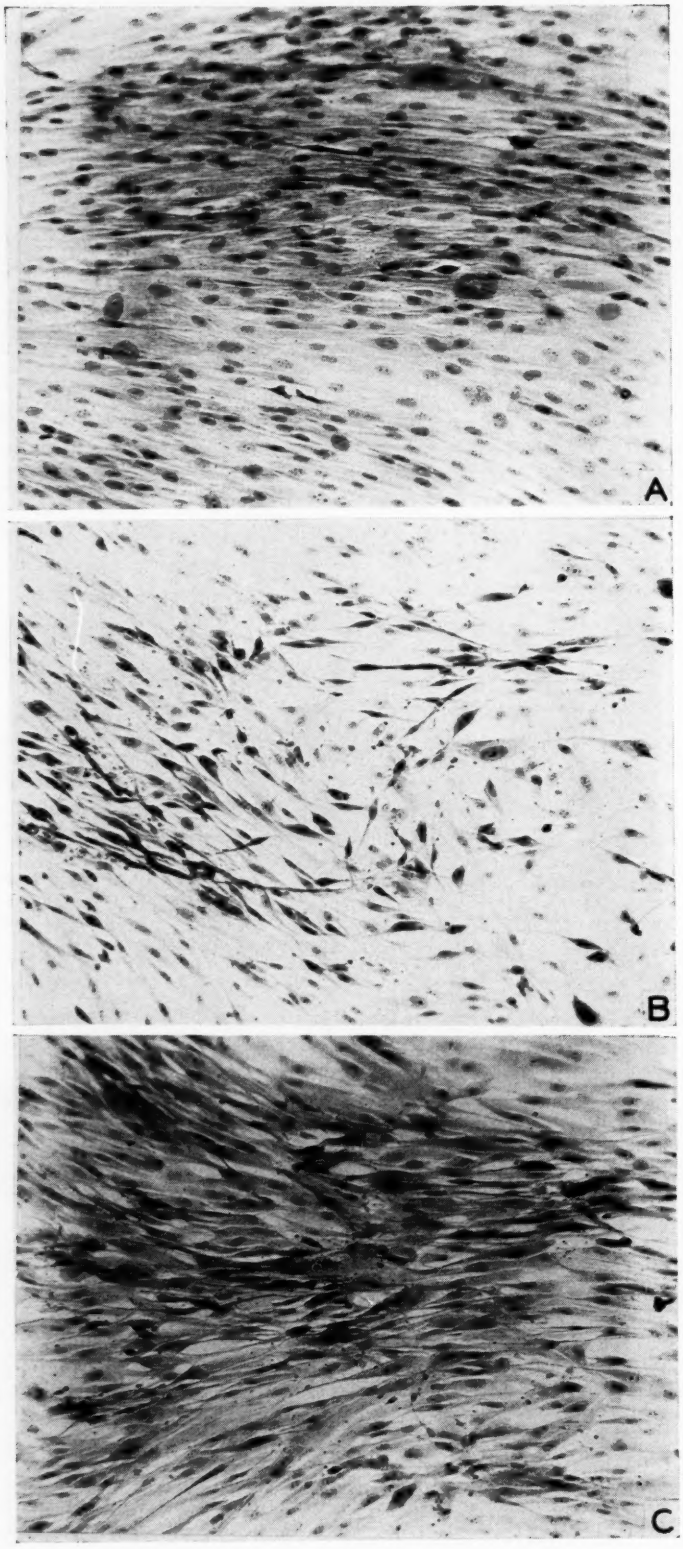

Fig. 4.—Higher magnification of cells in Fig. 3, illustrating the homogeneous spindle shape of uterine cells as compared with the irregular shape of fibroblasts. *A*, Myometrium, *B*, fascia, and C, myoma. (×145; reduced 2/7.)

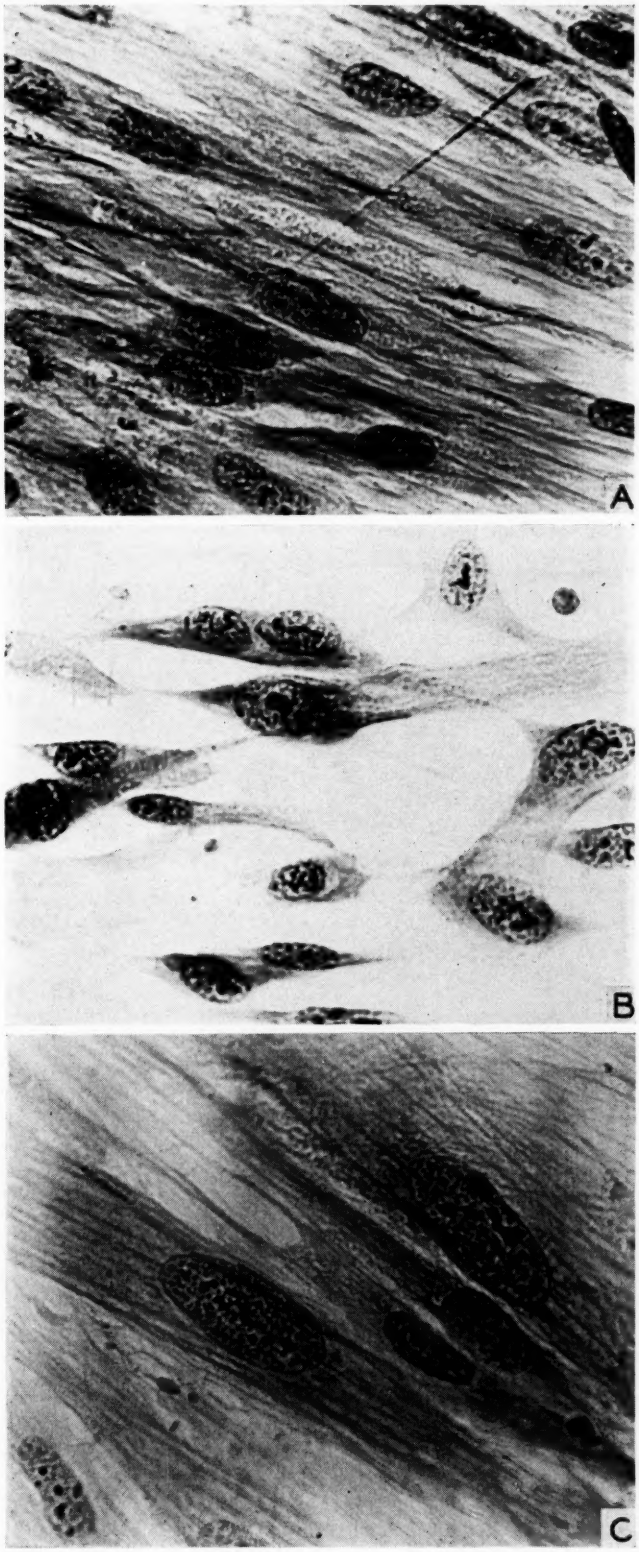

Fig. 5.—Higher magnification of cells in Fig. 4, showing the lateral adherent reticulum formation of uterine cells as compared with the rather loose network of fibroblasts. *A*, Myometrium, *B*, fascia, and *C*, myoma. (×930; reduced 2/3.)

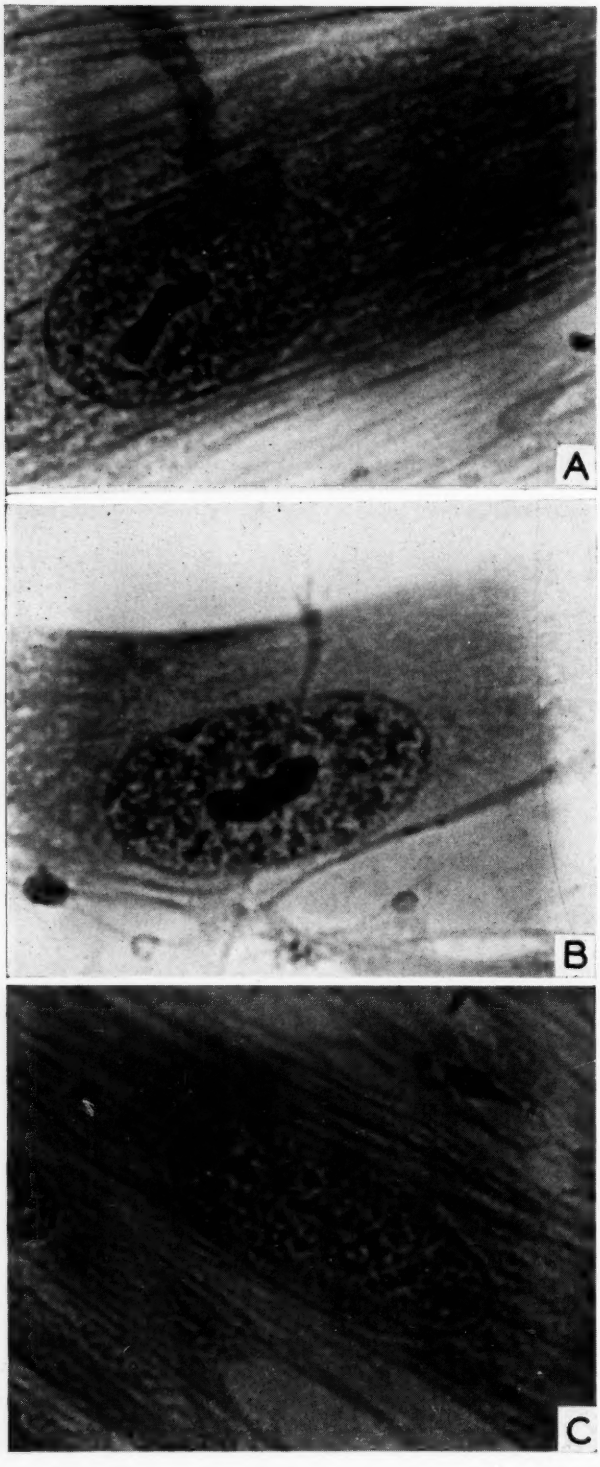

Fig. 6.—Higher magnification of individual cells in Fig. 5, illustrating the presence of characteristic longitudinal striations in uterine cells and their complete absence in the fibroblast. *A*, Myometrium, *B*, fascia, and *C*, myoma. (×1500; reduced ⅓.)

Although each of these observations strongly suggests that our myometrial and myoma cellular outgrowths are of smooth-muscle cell origin, unequivocal proof still remains to be demonstrated.

*Infrared Spectrophotometric Analysis of Original Tissue Specimens and Cultured Cells.**—

In search for proof that our cultural outgrowths were of smooth-muscle origin, we became interested in the possibility that uterine cellular preparations might give us a characteristic *myosin* absorption spectrum when studied by means of infrared spectrophotometry. Conversely, fibroblastic cultural preparations from fascia should not give a myosin spectrum but might produce a collagen spectrum even though we have never detected the presence of collagen in fibroblast cultures by differential staining methods. Curves *A* and *B* of Fig. 7, supplied by Dr. Wood, indicate that the spectra of myosin (rabbit) and collagen (exemplified by the collagen derivative, gelatin) are sufficiently characteristic between 7 and 8.5 microns for the two pure proteins to be distinguished unequivocally. In view of these results, infrared absorption spectra were recorded for specimens prepared from cultured cells as well as original tissue of 4 different patients. Typical results are presented in Fig. 7, curves *C* to *H*. It is evident that there is no significant difference between the absorption spectra of the cultured cells from the three different tissues. Similarly, however, the spectra of the three original tissues also show no significant difference.

Presumably, under the conditions of these experiments, the infrared spectrophotometric method is not sufficiently sensitive to detect differences either in original specimens of myometrium, myoma, and fascia or in cultured cells from these tissues.

Spontaneous and Induced Contraction Studies.—

The experiments presented in this section were performed on cover-slip preparations, mounted in a simple microscope-slide perfusion chamber.

One of the fundamental characteristics of muscle, whether cardiac, skeletal, or smooth, is its ability to contract when properly stimulated. Therefore, in our efforts to prove unequivocally that our uterine cellular outgrowths were smooth-muscle prototypes we made an extensive study of their contraction potential. Motion pictures of myometrial, myoma, and fascial cells, cultivated for short or long periods with or without chick-embryo extract, were taken at various time-lapse intervals. No evidence of spontaneous contraction was ever observed in any of these cell types. The next logical step was to attempt to induce contraction by various experimental means. Prior to starting this phase of the problem we decided that preliminary contraction studies with freshly excised strips of myometrium and myoma might give us some lead as to the best method of inducing contraction in cultured cells.

Specimens of myometrium and myoma were taken from 6 patients and strips approximately 4 to 6 cm. long and 5 to 7 mm. square were set up

*We are indebted to Dr. Darwin L. Wood of the Physics Department for recording the infrared spectra and aiding in their interpretation.

in a Kymograph recording apparatus. The contraction potential was tested by the application of various gases, drugs, and electrical stimuli. These experiments, performed by Dr. J. Poppy of our Department, will be reported in detail at a later date. The major finding pertinent to the present report, however, was that the best tonicity, contraction cycle, or rhythmical contrac-

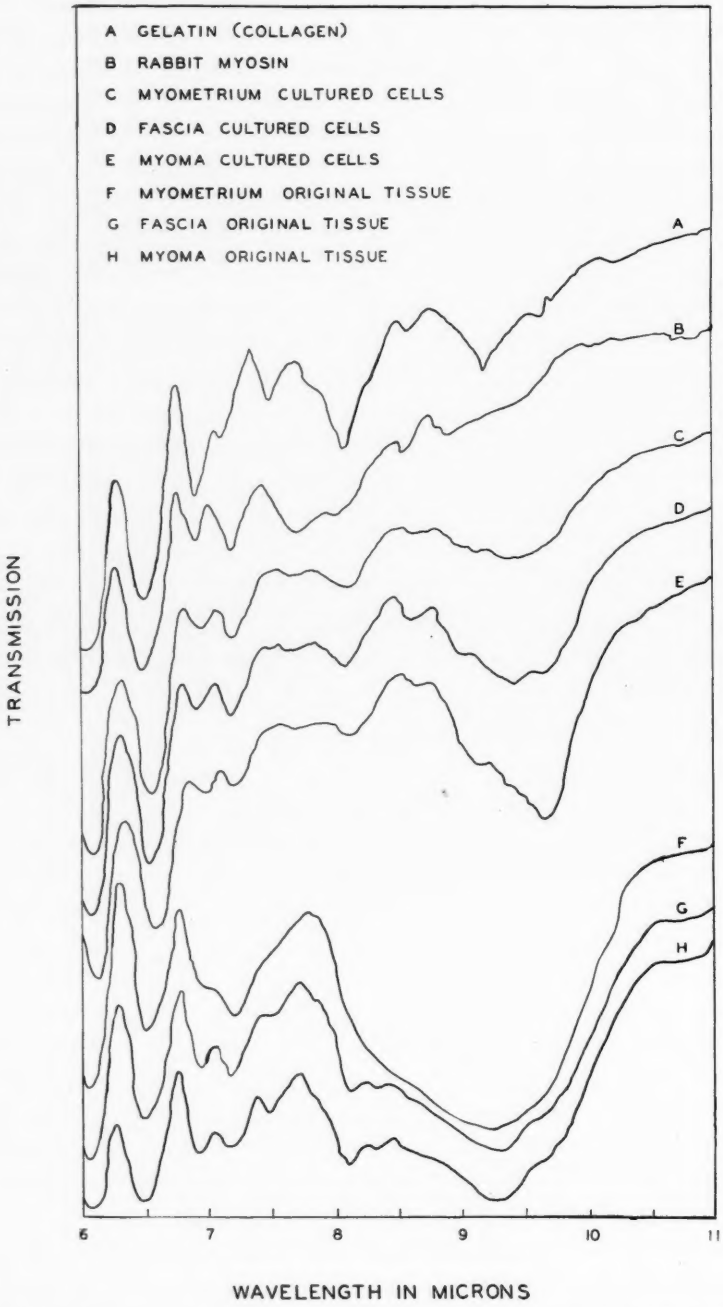

Fig. 7.—Infrared spectra of myometrial, fascial, and myoma cultured cells and of myometrial, fascial, and myoma original tissue.

tion was displayed by strips treated first by bubbling carbon dioxide and then oxygen through the balanced salt solution containing the uterine strips. The effect of carbon dioxide apparently was to relax the tissue, followed by oxygen which produced the contraction. Addition of a histamine solution (0.1 mg. per milliliter) during the bubbling of oxygen appeared to augment the rise in tonicity of the tissue. With the exception of Mecholyl chloride which gave an equivalent augmentation, other drugs were less effective in enhancing the effect of oxygen and when used in the absence of oxygen produced a much lower tissue response.

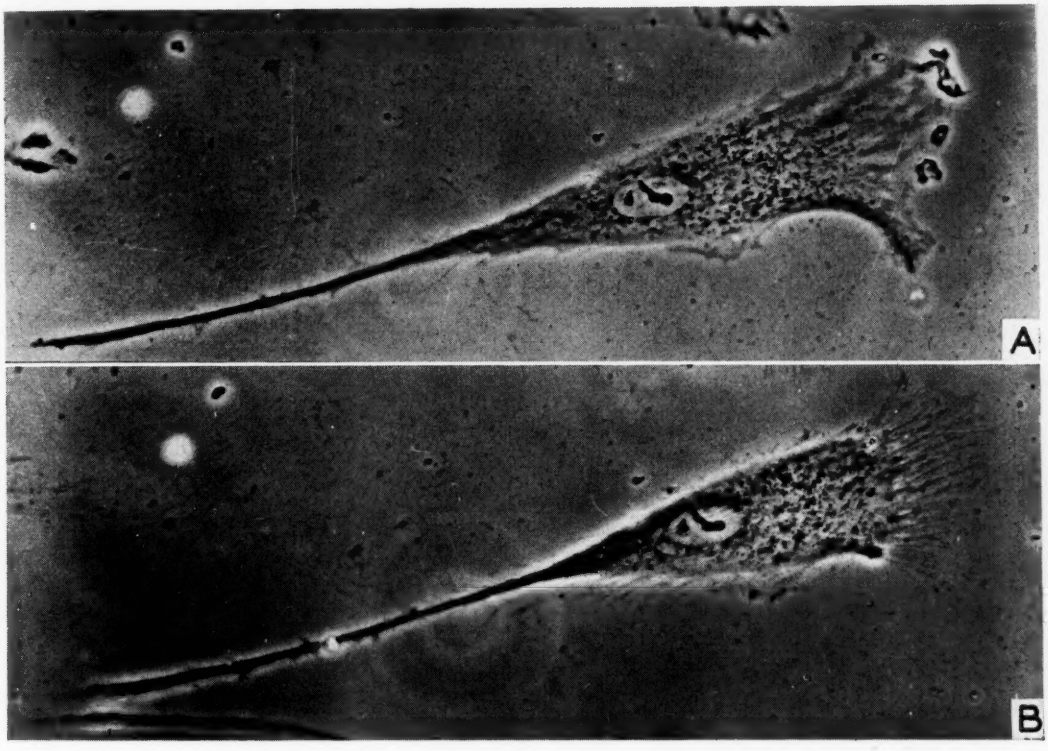

Fig. 8.—Contraction of living myometrial cell produced by ATP. *A*, In salt solution, and *B*, 15 minutes after the addition of 0.005 M ATP. Cell from the outgrowth of a myometrial specimen obtained from a 34-year-old patient at cesarean section. (×465; reduced ⅙.)

The next step was to transfer the knowledge we had acquired from tissue strips to our cultured cells. Experiments were therefore performed to determine the effect of perfusing a nutrient fluid saturated first with carbon dioxide, followed with oxygen, and finally with oxygen plus histamine (0.01 mg. per milliliter) on cultured myometrial, myoma, and fascial cells. Results were recorded by time-lapse cinematography. No evidence of contraction was demonstrable in any of the cell types. However, definite differences between the effects on uterine cells and fibroblasts were discovered in these studies. The perfusion of carbon dioxide saturated nutrient fluid had absolutely no effect on any of the cell types. On the other hand, the perfusion

of oxygen followed by oxygen plus histamine (0.01 mg. per milliliter) saturated nutrient fluid destroyed the fibroblasts but produced only the formation of an active, undulating membrane near the nucleus of the muscle cells.

At this point in the contraction work we resorted to testing all known contractile agents; first oxytocic agents like Pitocin and ergonovine maleate; second, general contractile drugs like epinephrine hydrochloride, eserine salicylate, Mecholyl chloride, histamine acid phosphate, collyrium pilocarpine hydrochloride, and adenosine triphosphate. The observations noted in these experiments can be briefly summarized as follows:

1. Dilute solutions of oxytocic and contractile agents appear to injure fibroblast cultures but have no effect on muscle cells.

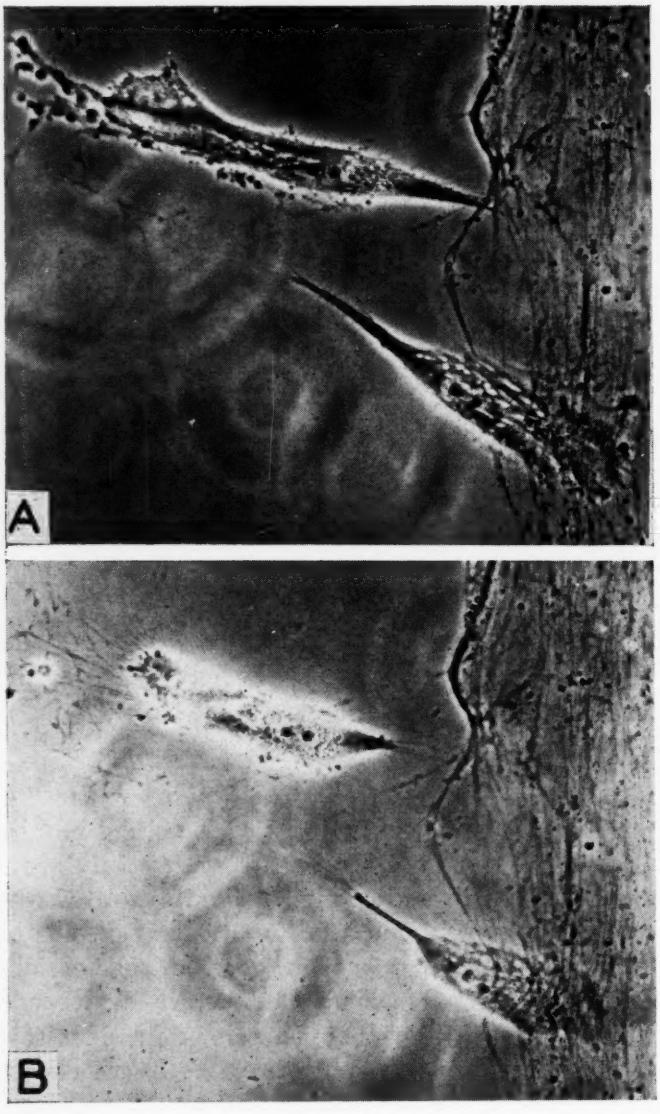

Fig. 9.—Contraction of living myometrial cells produced by ATP. *A*, In salt solution, and *B*, 15 minutes after the addition of 0.005 M ATP. Cells from the outgrowth of a myometrial specimen obtained from a 48-year-old patient at hysterectomy for myomas. (×310.)

2. Concentrated solutions of these drugs apparently destroy fibroblasts but are much less toxic to uterine cells.

3. In no instance was a recognizable contraction observed in these studies.

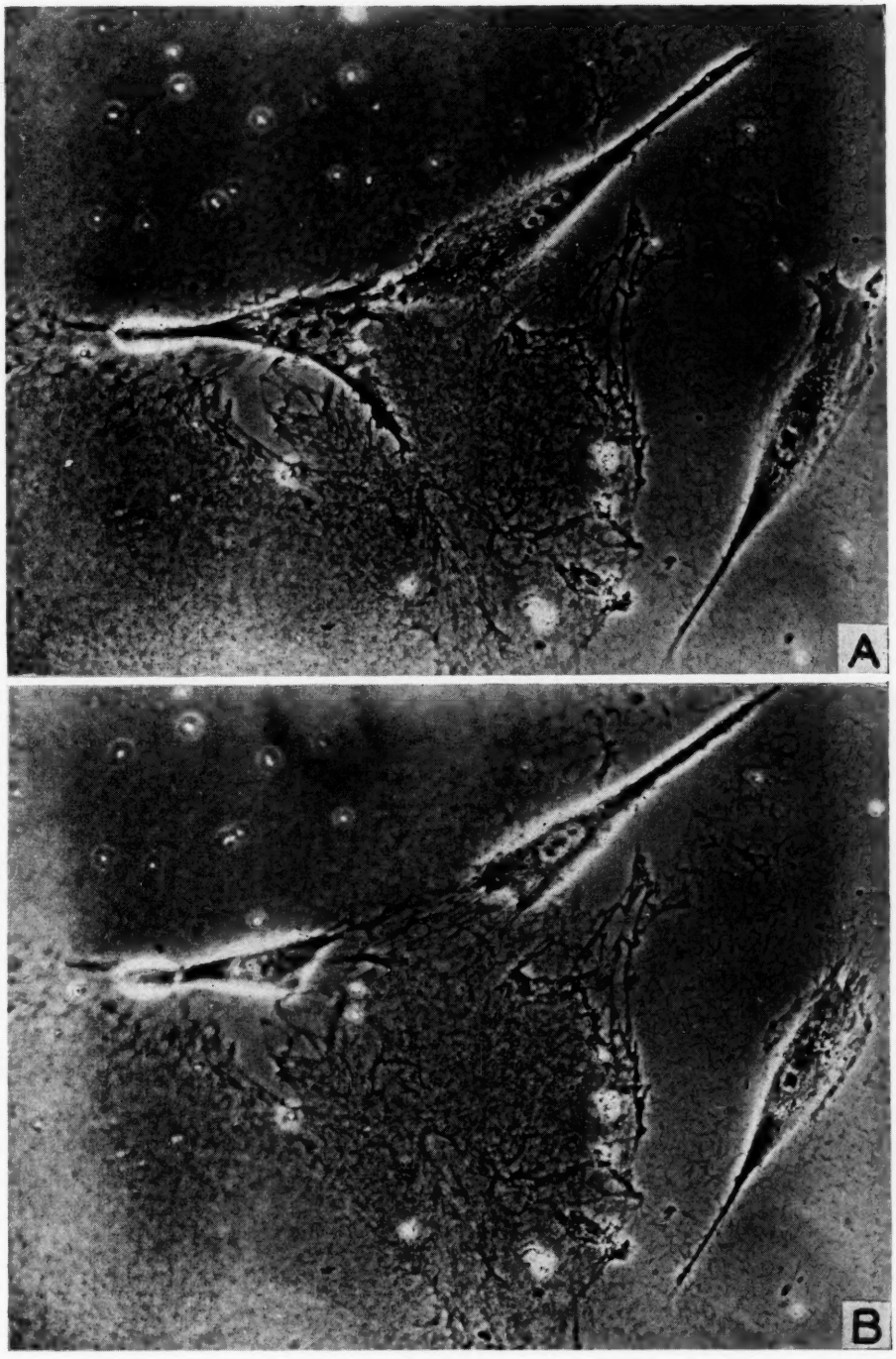

Fig. 10.—Contraction of living myoma cells produced by ATP. *A*, In salt solution, and *B*, 15 minutes after the addition of 0.005 M ATP. Cells from the outgrowth of a myoma specimen obtained from the same patient described in the legend for Fig. 9. (×310.)

Recently our attention was drawn to the contraction studies of Szent-Györgyi[17] using ATP with muscle fiber and thread models. It is apparent from his work as well as that of other workers in the field, that the activity of ATP in producing contraction of fiber and thread models depends on the presence of a proper concentration of magnesium and potassium ions. If this is the case with nonviable preparations, then one might suspect that a similar set of conditions would be required to make ATP active on living cells cultured in vitro. These ideas were brought out at a discussion of the contraction problem with Dr. L. Lorand, a former colleague of Szent-Györgyi. Since, in preliminary studies, the usual 0.05 M KCl and 0.001 M $MgCl_2$ salt solution used by investigators for nonviable muscle fiber and thread models was found to be hypotonic for our cultured cells, in collaboration with Dr. Lorand an isotonic salt solution consisting of 0.0014 M $MgCl_2$, 0.14 M KCl, and 0.0285 M $KHCO_3$, pH 7, was prepared and used in subsequent experiments.

The procedure followed was to prepare the microscope-slide perfusion chamber with this salt solution in place of the nutrient fluid. Then, a freshly prepared ATP-salt solution mixture (1:9) was perfused through the chamber (final ATP concentration 0.005 M). Definite contractions of varying magnitudes were observed in muscle cells approximately 15 minutes after the addition of ATP, as illustrated in Figs. 8 to 10. Unfortunately, however, this specific contraction criterion was not the answer to our identification problem because fibroblasts of fascial cultures also exhibited varying degrees of contraction upon the addition of ATP (Fig. 11).

A review of recent literature, meanwhile, disclosed that Hoffman-Bering and Weber,[18] working with nonviable water-glycerol extracted cultured cell models, were able to induce contraction of fibroblasts by adding ATP at a concentration of 0.002 M. Lettré,[19] on the other hand, noted only a rigidity of living fibroblasts from chick mesenchyme on the addition of 0.01 M ATP, which was reversible one hour after applying the nucleotide because of its degradation in the nutrient medium. Benitez, Murray, and Chargaff[20] observed that when ATP was incorporated in the nutrient medium at a concentration of 0.01 M it was rapidly and severely toxic to living adult rat fibroblasts. At 0.005 M, these workers found that ATP was not toxic and no effect at all was demonstrable at the end of 20 hours. These observations with *living* cells agree with our earlier findings in which ATP was found inactive when applied to cultures containing nutrient fluid or Hanks balanced salt solution. It is apparent from these studies that the contractile activity of ATP on living cultured cells is directly dependent on the presence of the proper physiologic concentration of magnesium and potassium ions, as was found to be true with nonviable cell, thread, and fiber models.

Furthermore, in agreement with the findings of Hoffman-Bering and Weber,[18] we have observed an irregularity in the number and size of living cells contracting within a single culture. Usually the smaller the cell the shorter the period of time before contraction occurs after ATP is added. Many large cells remain intact regardless of the length of perfusion or the concentra-

tion of ATP. As pointed out by Weber,[21] a cell can contract only if the diameter of the cell is small enough that the rate of ATP splitting is not limited by the rate of diffusion. This limiting factor of cellular diameter makes it extremely difficult to evaluate contraction differences between uterine muscle cells and fibroblast cultures. As mentioned earlier, muscle cells are generally larger than fibroblasts and consequently it is actually more difficult to induce

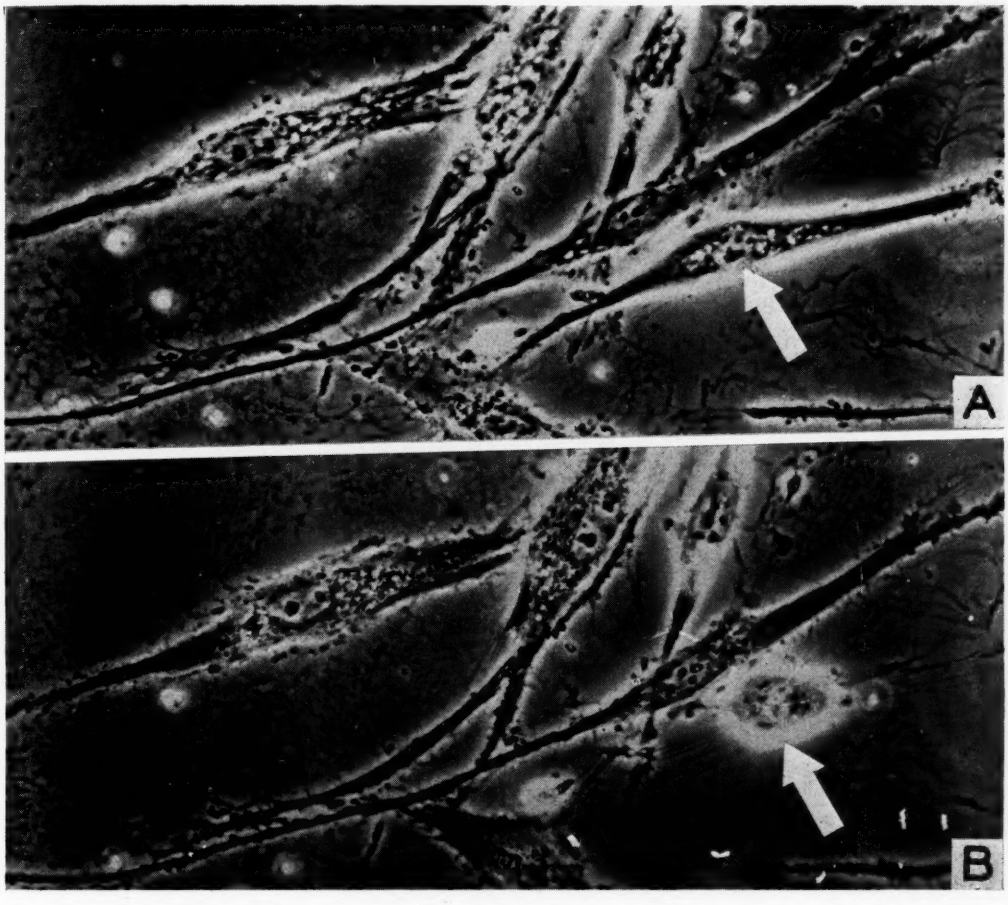

Fig. 11.—Contraction of a single living fibroblast produced by ATP. *A*, In salt solution, and *B*, 15 minutes after the addition of 0.005 M ATP. Cells from the outgrowth of a fascial specimen obtained from the same patient described in the legend for Fig. 9. (×355.)

contraction in the former than in the latter. Attempts to demonstrate a contraction difference between these cell types by employing a lower concentration of ATP (0.0033 M) were unsuccessful. At the present time we feel that further studies along these contraction lines would not be profitable. Possibly in our cellular outgrowths we may be dealing with an indifferent type of cell with the potential of forming a smooth-muscle cell in the case of uterine muscle or myoma, or the potential of becoming a fibroblast in the case of fascia. Growing in vitro, the cells may have reverted (anaplasia) to a common indifferent form and ap-

parently have many similar characteristics including the capacity of contraction. This becomes understandable when we recall that both smooth muscle and fibroblasts have a similar origin, namely, the mesenchyme.

Therefore, by present available methods it seems improbable that unequivocal proof of cellular origin can be demonstrated. The differences already noted between myometrial or myoma cells and fibroblasts, as presented in this report, however, warrant the conclusion that our uterine cellular outgrowths are smooth-muscle cells or at least their precursors. Therefore, we now feel justified in returning to our main problem of determining experimentally the stimulating and inhibiting effects of various hormone preparations on these uterine cells in vitro. In this manner we may eventually learn how to prevent or control the growth of myomas in vivo.

Summary

In an effort to gain a better insight into the origin and development of uterine fibroids and thereby ultimately approach the problem of preventing them or at least restraining their growth, we have undertaken to grow and observe myoma (fibroid) cells in vitro.

As a first step in this far-reaching program it was necessary to develop appropriate cultural techniques. This accomplished, the problem of positive cell identification became an important hurdle to further work.

While not all aspects of these problems have been completely disposed of, we have reached a point where it is possible to grow and study in vitro uterine muscle cells, or prototypes thereof, in sufficient quantity to permit undertaking a third important phase of this investigation dealing with growth stimulation and/or growth restraint.

This third phase of our study will serve as the basis for a future report on the growth and development of uterine fibroids.

Grateful acknowledgment is made to Mrs. Sylvia Kleanthous for technical assistance in this study.

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Discussion

DR. DANIEL G. MORTON, Los Angeles, Calif.—It is of considerable interest that, in tissue culture, fascial explants grow fibroblasts and that explants from myomas seem to grow smooth-muscle cells. The fact that the cultured cells cannot be distinguished with relation to contractility responses throws some doubt upon their separate identity, or perhaps suggests that both types of cells may have a common prototype.

Another point of interest is the ability to grow such tissue at all from presumably normal and/or benign structures, a situation which is at variance with cultures of tissues from epithelial structures where only the cancer or precancer cells can be grown.

In considering the question of the origin of fibroids, it seems necessary in the future development of Dr. Miller's experiments to bear in mind the possibility that fibroids may arise from muscle cells in the walls of the myometrial arteries, as Otto Schwarz and others have suggested. An attempt to culture cells from this source would seem to be in order. It would be of the greatest interest, if such cells could be cultured, whether or not they were like those grown from fibroids.

The enormous amount of work which has been done already has actually yielded no more than a small amount of information to date. It may well be that after still another enormous amount of work Dr. Miller and his associates will conclude their research without having obtained a shred of information regarding the original aim of the investigation. Meanwhile, however, he will have made certain fundamental observations regarding the behavior of specific cells in tissue culture, and their response to various agents. Whether or not these observations have a bearing on the origin and development of fibroids, it is possible that they will have other important and entirely unlooked-for implications. In fact, many of the world's greatest medical discoveries have been made in this manner. This is the very essence of research. We should all be willing, more often than we are, to seek information for information's sake and to be less concerned with the immediate utilitarian aspects of our researches. Particularly is this true, I believe, for those of us (the majority of us) who are concerned with the education of students of medicine. It is a point of view which young men in medicine should ever have before them, for it serves to stimulate and captivate the imagination. Unfortunately it is a point of view which medical men tend to lose early and often completely.

DR. EMIL NOVAK, Baltimore, Md.—If Dr. Miller could do nothing more than furnish us with a sure way to differentiate muscle cells from fibroblasts in tissue culture work, this would be a significant contribution, this having always been a *bête noire* in such investigation.

A prevalent and much publicized theory concerning the etiology of fibroids is that they are produced by estrogens. This may possibly be true, but the evidence for it has always seemed to me to be pretty flimsy. The two authors usually brought forward in proof of this hypothesis are Witherspoon and Lipschutz. The former's arguments are altogether circumstantial and often grossly incorrect. For example, the ovaries found with fibroids of the uterus are often entirely normal, with normal ovulation and progesterone production, and are not merely estrogen-producing organs, as Witherspoon almost implies. Again, the fact that uterine myomas usually regress after menopausal cessation of ovarian function may be due to lessening of the blood supply rather than to withdrawal of any specific effect of estrogens. Incidentally, Robert Meyer was always of this belief.

Again, it is often irritating to see the work of Lipschutz and his associates quoted in support of the estrogenic etiology of uterine fibroids. These authors themselves disclaim any such intention. In their brilliant experiments, they have shown the tumorigenic effects of estrogen in certain laboratory animals, more particularly guinea pigs, in which estrogen administration can produce large fibromas—never myomas—in the cellular tissue of the pelvis and abdomen. A good many years ago I visited the clinic of one of our own Fellows, and was asked by one of his associates to come to the laboratory to see the uterus of a monkey in which myomas had been produced by estrogens. This uterus looked almost like one covered with miliary tubercles, all of which under the microscope were pure fibromas, with no muscle tissue at all. Nor was there any sign of any tumor in the myometrium. It is true that in a very few reported experiments, like that of Nelson, small myomas were found after estrogen administration, but such observations are so few that it would seem difficult to exclude the possible occasional spontaneous occurrence of such nodules in monkeys. I certainly hold no brief against the possible role of estrogens in the production of uterine myomas, but I would wish for more impressive evidence on this point than is as yet available.

DR. MILLER (Closing).—I am very much impressed by muscle contraction. Methods now available give us a means for studying muscle not only with reference to the fibroids but also with reference to the function of the uterus during labor. It is possible to take "dead" muscle strip and under appropriate stimulation make it contract. This is a chemical reaction. I wonder if this work does not bring us just a little closer to the thinking of The chemical reaction which takes place in the body may take place even in dead tissue that famous scientist who propounded the theory of relativity? Everything is relative. outside the body. Perhaps life and death are relative—only the speed of light is constant.

A CRITICAL SURVEY OF PRESENT METHODS OF DIAGNOSIS AND THERAPY IN HUMAN INFERTILITY*†

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MANY physicians interested in problems of infertility have a growing impression that some of our diagnostic tests and many of our therapeutic activities for this condition do not provide the information or produce the results that we hopefully think they do.

This has been especially true in England where the literature concerning infertility problems has frequently contained expressions of skepticism about diagnostic and therapeutic techniques. To mention but a few of these, Stallworthy[1] in 1948, writing on "Facts and Fantasy in the Study of Female Infertility" (certainly a very apt title), reviews 1,000 cases, with a 35 per cent pregnancy rate, but is dubious as to whether any investigation or treatment of these couples had much to do with the resultant success. Dr. John Rock,[2] in this country, has frequently expressed the same thought.

In a review of 700 consecutive traced cases from his clinic in Liverpool, Bender[3] found a conception rate of 46.3 per cent. In his analysis of these cases, however, he concluded "that at least half, and probably more, of the conceptions were unrelated to medical treatment."

Jeffcoate[4] considers this subject "to be obscured by clouds of fantasy, wishful thinking, false promise and quack remedy, as much today as it was in the days of love potions and fertility amulets." That he may not be far wrong is well exemplified by the history of a patient seen recently who stated that while under treatment for their infertility problem in France, her husband received a number of injections of an extract said to have been made from the testis of the Tibetan musk ox.

Therefore, a decision was made to review the infertility cases registered during the years 1946 to 1953 in the Sloane Hospital Sterility and Endocrine Clinic and the private practice of one of us (C. L. B.) in an attempt to find some relationship between investigation, treatment, and pregnancy.

A total of 1,607 couples was thus reviewed; of these it was possible to get a follow-up on 1,213, or 75.4 per cent. Their sterility status and pregnancy rate are demonstrated in Table I.

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TABLE I. STERILITY STATUS AND PREGNANCY RATE IN TOTAL GROUP OF 1,607 PATIENTS

	TOTAL	FOLLOWED	PER CENT	NO. OF PREGNANCIES IN FOLLOWED CASES	PER CENT
Patients	1,607	1,213	75.4	444	36.6
Primary Sterility.—					
Private	342	270	78.4	110	40.7
Clinic	666	498	74.8	156	31.5
Secondary Sterility.—					
Private	134	108	79.1	42	38.9
Clinic	465	337	72.4	136	40.3

In considering different ways to try to correlate ultimate reproductive destiny with previous investigation and treatment, the authors immediately became involved in all kinds of variables and situations where classification was difficult if not impossible and even misleading.

It occurred to us that, as a preliminary screening measure, it would be an advantage to find whether local organic pathology in the woman identified at the first physical examination would prove to be an infertility factor. In other words, could an impression of the fertility potential of these patients be made even before diagnostic procedures were begun.

TABLE II. PERCENTAGE OF PREGNANCIES IN CASES WITH VARIOUS ABNORMALITIES FOUND ON PHYSICAL EXAMINATION

	CASES	NO. OF PREGNANCIES	PER CENT
Minor abnormalities (cervicitis, malposition, or both)	296	125	42.25
Uterine pathology (fibroids, malposition, cervicitis, or combinations of these)	97	36	37.1
Adnexal pathology (pelvic inflammatory disease or proved endometriosis)	158	53	33.6
Multiple major abnormalities (including congenital)	90	16	17.7

Table II demonstrates that, when percentage of subsequent pregnancies is considered, multiple major abnormalities and tubal pathology are the basic local organic pathological factors in infertility in the female.

TABLE III. COMPARISON OF PREGNANCY RATES IN PATIENTS WITH AND WITHOUT PHYSICAL ABNORMALITIES ON FIRST EXAMINATION

	TOTAL	NO. OF PREGNANCIES	PER CENT
Cases with negative findings on physical examination*	573	214	37.3
Cases with demonstrable physical abnormalities	640	230	35.9

*Many of these patients later had abnormal findings on diagnostic work-up.

Naturally, when multiple major pathological findings occur, including congenital abnormalities, it is not surprising that the pregnancy rate is low. When all cases of local pathological conditions are considered as a group,

however, it is interesting to note that their ultimate pregnancy rate is practically the same as that of the group of patients in whom no abnormalities were observed on original examination (Table III), and this, incidentally, is regardless of whether or not they were treated. Treatment of these abnormalities has not resulted in any great pregnancy success.

As a result of this, we decided to concentrate our observations on the results of the usual various diagnostic tests to which each couple is subjected. To do this we placed each investigated couple in a category by means of a grading technique, according to what we thought their degree or severity of infertility was. For instance, we gave to a couple in whom we could find no identifiable source of infertility a grade of first-degree infertility; whereas a couple in whom there was what we considered to be an absolute source of sterility was designated as having fourth-degree infertility. Those couples with abnormalities conventionally thought to contribute to infertility were graded second or third degree, according to the number and severity of their abnormalities (Table IV). Since preliminary pelvic organic pathology, except for multiple abnormalities and pelvic inflammatory disease, was not a factor in the reduction of the fertility rate, these were not included in grading techniques, but results of diagnostic tests were graded as indicated.

TABLE IV. ARBITRARY GRADIENTS OF INFERTILITY

NO IDENTIFIABLE ABNORMALITY	CONDITIONS THOUGHT TO CONTRIBUTE TO INFERTILITY CLASSIFIED ACCORDING TO RELATIVE SEVERITY		ABSOLUTE INFERTILITY
FIRST DEGREE	SECOND DEGREE	THIRD DEGREE	FOURTH DEGREE
♀	♀	♀	♀
Tubal patency—good p.c. test Normal ovulation Normal ancillary tests	Questionable tubal patency Ovarian dysfunction (occasional anovulation, inadequate secretory phase, abnormal temperature chart, etc.)	Tubal closure First- or second-degree amenorrhea Multiple physical abnormalities	Surgical or congenital absence of tubes, ovaries, or uterus
♂	♂	♂	♂
Normal sperm count Normal ancillary tests	>20,000,000 but with poor progression, motility, or abnormal forms <20,000,000	Azoospermia	Congenital abnormalities Absence of genitals

These classifications are then analyzed in terms of percentages of the total infertility population examined and also in terms of subsequent pregnancies. In this way it was hoped that we could test whether or not the various conditions which are now conventionally thought to be infertility factors actually do contribute to infertility—or whether these impressions are just another medical fantasy.

Admittedly these are arbitrary classifications, and unquestionably every physician who works in this field would produce individual variations—in fact, we ourselves had disagreements concerning the categorical spot in which to

place certain conditions. When we considered, from our punch-card system on each patient, the forty-odd available diagnostic factors thought to contribute in some way to infertility, and then considered the infinite number of variables with these diagnoses, we almost discarded the whole idea. As the cases began to get sorted out, however, it was possible to pigeonhole them with a reasonable degree of identification.

The 1,213 patients on whom we could obtain complete follow-up were then assorted, according to our grading system, into the various groups described. These groups, since they represent what we assume to be evidence of increasing hindrance to fertility, should have an ever-decreasing incidence of pregnancy. In other words, theoretically all couples with first-degree infertility should produce a pregnancy, and no fourth-degree couples should, with an ever-decreasing incidence of pregnancy in between. Fig. 1 demonstrates whether or not this concept is a valid one. Since fourth-degree cases were considered incurable they were not included in this chart.

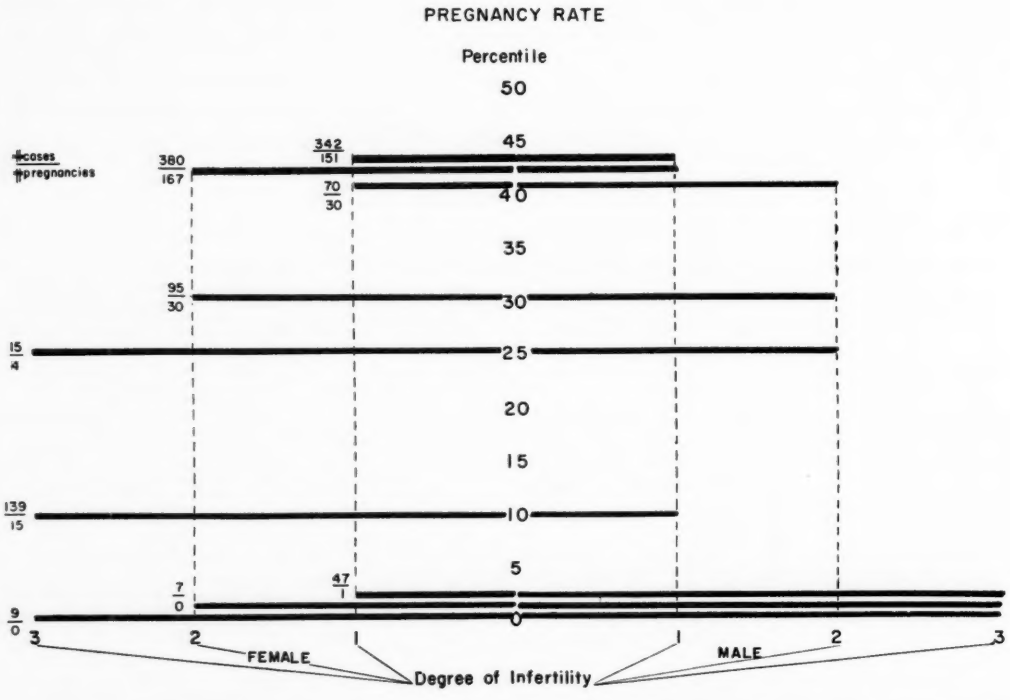

Fig. 1.—The vertical line represents the percentage of pregnancies in each group and the horizontal lines represent, by their length, the degree of infertility of the female or male partner, the former being to the left of the percentage line, the latter to the right. The numbers represent the patients in each group over the pregnancies in each group.

Representations of quality and quantity of infertility are somewhat confusing because there are two patients who constitute a "case" instead of one. Therefore an attempt was made in Fig. 1 to differentiate between the male and female factors and also to provide some quantitative estimation of each. The vertical line represents the percentage of pregnancies in each group and the horizontal lines represent, by their length, the degree of infertility of the female or male partner, the former being to the left of the percentage line, the latter to the right. The numbers represent the patients in each group over

the pregnancies in each group. It is quite noticeable that reasonably minor degrees of infertility in either partner do not greatly reduce the fertility rate. A combination of minor factors does, however, and of course any combination with a major factor involved, in either sex, reduces it still further. That major factors in the female are apparently less of an ultimate hindrance to pregnancy than those in the male is shown by the greater percentage of pregnancies in these areas. There was only one pregnancy in the cases of male azoospermia, all therapy notwithstanding.

One group for whom there was no space on this already too complicated chart consists of 101 couples in whom, for various reasons, neither partner was investigated except for history and physical examination. Forty-six, or 45.7 per cent, of these became pregnant, this high degree of success undoubtedly being due the fact that one of the main components of this group was couples who became pregnant before any opportunity for investigation presented itself.

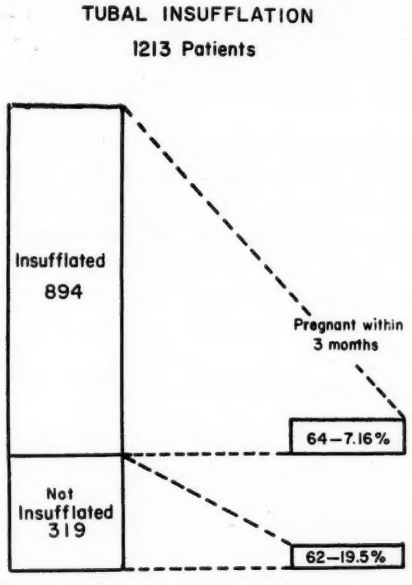

Fig. 2.—Occurrence of pregnancy within 3 months of insufflation compared with the occurrence in the noninsufflated group within 3 months of first visit to clinic.

The next aspect of the investigation of these cases concerned a consideration from a somewhat different point of view.

It has been frequently stated by others, and it is our impression, that the ordinary diagnostic tests used in infertility problems, especially tubal insufflation, may have therapeutic value. In an attempt to test the validity of this impression, the immediate results following various tests were evaluated.

Of 894 patients who had insufflations, for instance, 22 patients became pregnant during the same menstrual cycle, 29 in the next cycle, and 13 in the third (Fig. 2). Since this number who had pregnancies in 3 months is only a small percentage (7.16 per cent) of the total patients insufflated, this procedure would not seem to have a very significant therapeutic value. This is further emphasized by the fact that, of 319 patients not insufflated for some reason, 62, or 19.5 per cent, became pregnant within 3 months of their first visit. If the pregnancies occurring during the first two months, in the insufflated cases, i.e., 51 out of 894, or 5.7 per cent, were extrapolated over a year, for instance, the pregnancy rate would be quite appreciable, but so would the rate during any given month in patients who were not insufflated.

It may be interesting to compare, in this connection, Shields'[5] results in a small series of cases of artificial insemination. More patients who had not had a tubal insufflation done became pregnant within the first month than those who had had one insufflation, and of 10 patients who had had multiple insufflations only one became pregnant during the first month of inseminations.

Similarly, of 180 patients who had salpingograms, 3 became pregnant in the same cycle, 10 in the next cycle, 3 in the third; also exactly 10 per cent.

Considering this idea from a slightly different point of view, however, it is interesting to observe that of 33 followed patients whose tubes were closed to insufflation and who had no other tubal tests, 6, or 18 per cent, became pregnant. Of 102 patients with diagnoses of definitely closed tubes by salpingogram, 7 became pregnant. Thirty-five of these patients had tubal plastic procedures with two pregnancies, or 5.6 per cent success (if percentages are permissible with such small numbers), whereas, of the 67 patients who fell into what was thought to be this definite category of tubal closure, 5 became pregnant without operation, a percentage of 7.46!

In our Clinic, tubes are considered to be closed in patients who have no evidence on salpingogram of peritoneal spill of iodized oil after twenty-four hours.

It may not be quite reasonable to conclude that because of these figures, tubal plastic operations are useless and should be discarded, but it does imply that the techniques we use, in our Clinic at least, for the identification of tubal closure, could stand some improvement. If we diagnose definite tubal closure in a group of patients, 7.46 per cent of whom become pregnant anyway—surely there is something wrong with our diagnostic technique!

To continue on to another possible source of infertility, there were 244 patients who had what might be considered ovarian dysfunction—first- or second-degree amenorrhea, anovulation, or inadequate secretory endometrium (Fig. 3).

Ninety-seven of these, for various reasons, received no treatment for ovarian dysfunction but were followed for varying amounts of time. Measuring from the time they first appeared in the Clinic, 15, or 15.5 per cent, became pregnant within 3 months, 19, or 19.2 per cent, within 6 months, and 51, or 51.2 per cent, eventually.

The remainder of the 244 patients with ovarian dysfunction, amounting to 147, were treated in various ways, many repeatedly with different types of therapy. Of these, 124, or 84.4 per cent, were considered to be treatment failures because they did not become pregnant during treatment or within 3 months after cessation of treatment; 23, or 15.6 per cent, became pregnant during treatment or within 3 months after treatment was stopped.

Of the treatment failures, subsequent follow-up disclosed that 23 of these, or 18.5 per cent, ultimately became pregnant anyway, resulting in an ultimate pregnancy in 46, or 31.3 per cent.

Two things should be considered when examining this comparison. The first is that these two groups, the treated and the untreated, do not represent the statistician's ideal of alternate but exactly similar cases. Treatment was suggested to all patients, and 97 were untreated in practically every instance either because pregnancy occurred before treatment could be started or because of the patient's own choice. After all, in suggesting various types of therapy, the physician either in the clinic or the private office could not too enthusiastically recommend a course of treatment, the results of which were problematical, and no attempt was made to persuade patients to take treatment who were not anxious to do so.

The other aspect of this comparison to be considered is the fact that a large number of the treated patients received many different kinds of treatment. There is always, in infertility groups of this kind, a residue of patients anxious to try any new type of therapy, however remote the hope of success, and our Clinic is no exception.

Limitations of time and space prevent any description of the types of hormone therapy used. Suffice it to say that most of the "enthusiasms" of other workers in this field during the years in which the series was collected (1946-1953), and a few of our own, were tried out repeatedly and hopefully. Steroid-induced artificial cycles, one gonadotrophin after another as they emerged from the preclinical laboratories, thyroid therapy, combinations of various sorts—these were all used—probably in much the same way that these substances were assayed in other infertility and endocrine clinics throughout this country and abroad.

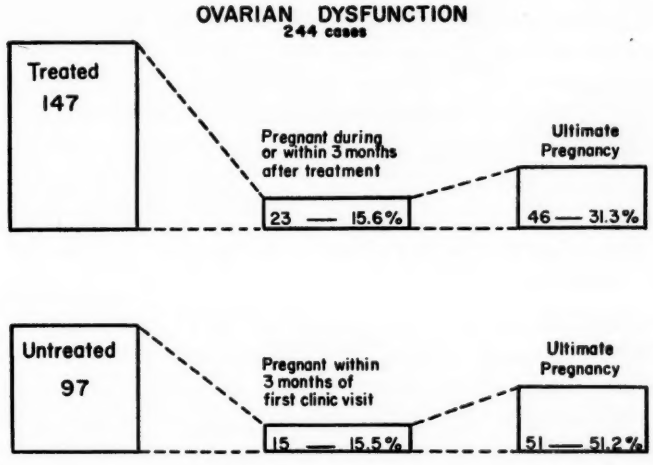

Fig. 3.—Comparison of the occurrence of pregnancy in the treated and untreated cases of ovarian dysfunction.

Not only in the cases of ovarian dysfunction just discussed, but also in other types of investigation and treatment for other infertility factors, we must assume that, as each test or treatment is being evaluated for its therapeutic effect, the subsequent history of the couple must be considered as though they were making a fresh start on their reproductive career, and their course therefore compared to the reproductive performance of couples who are not considered infertility problems.

To do this, the conception time in planned pregnancies must be considered. Tietze, Guttmacher, and Rubin[6] provide data on this in 1,727 cases, and Whitelaw,[7] in a smaller group of 250 cases. In the former series, 61.3 per cent, and in the latter, 69.2 per cent of the couples became pregnant within the first 3 months. Therefore, presumably, the best that can be expected of any type of therapy, within the first 3 months, is that about two-thirds of the couples become pregnant. Furthermore, these and other series leave a residue of about 10 per cent nonpregnant patients after a year of attempted pregnancy, and this residue is the group from which is drawn the population considered in this study.

Since the condition of the cervix was not found to be a statistically significant factor in sterility, it will not be considered extensively here.

Suffice it to say that, in this series, more patients with cervicitis became pregnant who were not treated than those who were, the treatment being cauterization. Also, as has been reported elsewhere,[8] the concept of a cervical bacterial barrier as an infertility factor is, in the light of our present knowledge, probably not a tenable one, even though we can justifiably make the assumption that certain bacteria are definitely spermicidal in vitro.

The final subject for analysis was the potential fertility of the husband as determined by sperm count. Here was a test which obviously has no therapeutic value.

Table V shows a correlation between gradations of semen quality and potential fertility as determined by subsequent pregnancies. Except for a dip in the third category, it does not seem to make much difference statistically what kind of a specimen a man has until his count gets below 20,000,000 per cubic centimeter with sperm of poor quality. At this point his potential fertility is greatly reduced.

TABLE V. QUALITY OF SEMEN IN RELATIONSHIP TO PREGNANCY

QUALITY OF SEMEN	TOTAL NUMBER OF CASES	CASES FOLLOWED	PREGNANCIES	PERCENTAGE
Count above 20 million, good motility, good progression, and/or good postcoital test	859	725	292	40.2
Count above 20 million, either poor motility or poor progression, not both	71	66	27	41.0
Count above 20 million, poor motility and progression or Counts below 20 million, with good progression and motility	118	90	24	26.6
Counts below 20 million, with either poor motility or poor progression, but not both	45	32	13	40.6
Counts below 20 million with both poor progression and poor motility	29	19	0	0
Azoospermia	72	44	1	2.3
Semen not evaluated		237	87	36.7
Total		1,213	444	

Comment

The first suspected but still somewhat surprising fact arising from this review was that, with the exception of multiple physical findings and pelvic inflammatory disease, local organic pathology in the female did not seem to have much to do with infertility. Cervicitis, malposition of the uterus, fibroids, uncomplicated endometriosis—none could be incriminated statistically as an infertility factor and, since this was true, it should follow that treatment of these conditions in order to alleviate infertility should be of no benefit. This proved to be the case. When cervicitis was treated by cauterization, for instance, fewer patients became pregnant than in the group that was left alone.

An evaluation of infertility factors, determined by the usual tests, showed that when minor factors occurred in one partner only, there was no deterrent to fertility, but where both partners had second-degree abnormalities fertility potential was reduced. Persistent azoospermia in the male proved to be the

most severe and consistent deterrent to fertility, whereas major factors in the female such as closed tubes or amenorrhea occasionally seemed to correct themselves, or rarely were amenable to treatment. The results of treatment of these conditions, however, were not as good as the results when patients were left alone.

If it is possible to conclude anything from one series of cases from one clinic, we may assume, then, that present techniques for the *investigation* of infertility are of considerable value to us in determining the status of the infertile couple—although even these techniques would stand considerable improvement.

On the other hand, our present techniques of *therapy* for the major causes of infertility are totally inadequate. There is some question, however, as to whether the problem of infertility is susceptible to rational statistical analysis because of the extraordinary number of known variables affecting this condition, combined with an undoubtedly large number of unknown imponderables, producing an almost limitless number of possible combinations resulting in a situation almost as bad as the well-known monkey with the typewriter writing Shakespeare. In other words, in our present knowledge of this subject, we are not in a position to be categorical and it is doubtful whether we should conclude, for instance, that cervicitis should never be considered an infertility factor just because more untreated patients with cervicitis became pregnant than treated ones.

Therefore, we do not suggest discarding entirely our present concepts concerning the investigation and treatment of the infertile couple but rather we wish to point out the possible unreliability of these concepts and to enter a plea that they be viewed in a critical fashion. In this situation, as in other medical problems, there is a great fallacy in "post hoc ergo propter hoc" reasoning.

We do not expect to discontinue, in our Clinic, the investigation and treatment of the infertile couple because of the findings of this study. The purpose of this paper is, as its title implies, an attempt at a critical evaluation of our experiences in this field over a period of years.

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Discussion

DR. BAYARD CARTER, Durham, N. C.—Dr. Buxton has drawn to our attention the manifold imponderables we must consider in evaluating our techniques and results in infertility surveys. We agree that the studies done for infertility may be of considerable value, and may in certain patients have true therapeutic effects. Our present therapeutic measures for the treatment of infertility are frequently unsatisfactory and even futile.

The authors' statement that "with the exception of multiple physical factors and pelvic inflammatory disease, local pathology in the female did not seem to have much to do with infertility" finds ready acceptance by us. Cervicitis, malpositions of the uterus, myomas, uncomplicated endometriosis, and cystic ovaries could not be incriminated statistically as infertility factors.

In our first series of 500 couples, 110 patients with cervicitis had a higher pregnancy incidence than did the entire group. These patients with cervicitis also had a higher pregnancy incidence than did 49 patients who had had elsewhere cervical operations for the cervicitis before starting the infertility survey. The 104 patients who had retrodisplacements had a higher pregnancy incidence than did 35 patients who had had elsewhere some type of suspension operations. The 44 patients who had chronic adnexitis showed a pregnancy incidence which was practically identical to that of 22 patients who had had elsewhere operations upon the tubes. In 44 patients with unilateral or bilateral cystic ovaries, the incidence of pregnancy was higher than it was in 53 patients who had had elsewhere operations for cystic ovaries. In our group of 500 couples, therefore, all operations upon the women seemed to be associated with a decrease in the incidence of pregnancy. These observations were reported in *The Journal of the American Medical Association* in 1952.

We are also in full agreement with the authors' statement, "If it is possible to conclude anything from one series of cases from one clinic, we may assume, then, that present techniques for the *investigation* of infertility are of value to us in determining the status of the infertile couple—although even these techniques would stand considerable improvement."

Can these problems be subject to rational statistical analyses since the number of variables makes analyses unreliable? Can we accept the statement that major factors in the female are apparently less of an ultimate hindrance to pregnancy than are factors in the male?

We do not believe that these problems can be subject to rational statistical analyses. We do believe, however, that we may accept the statement that factors in the male cause more hindrance to pregnancy than do factors in the female.

In our last series of 750 couples, who did continue through the entire infertility survey, we divided the couples into two main groups; the first group was called the "good prognosis" group; the second group was called the "poor prognosis" group.

We also put in such variables and imponderables as (1) race; (2) years of presumed infertility; (3) "primary" and "secondary" infertility; (4) psychosomatic evaluation; (5) previous infertility studies elsewhere; (6) length of time from completion of survey to time of pregnancy; (7) relation of adoption to pregnancies subsequent to adoption.

These represented but a few of the variables and imponderables we had to consider. Briefly summarized, our findings may be stated:

1. Race.—The pregnancy incidence in the Negro couples was approximately one-third the pregnancy incidence of the white couples in both the poor prognosis and good prognosis groups.

2. Years of Presumed Sterility.—The length of time of presumed sterility reduced the incidence of pregnancy in both the good and poor prognosis groups.

3. Primary or Secondary Infertility.—Couples with primary or secondary infertility showed practically the same incidence of pregnancy in "good prognosis" couples. A slightly higher incidence of pregnancy was found in the poor prognosis group with secondary infertility.

4. Psychosomatic Evaluation.—There was a slightly higher incidence of pregnancy in the psychosomatically "adequate" group.

5. Previous Infertility Studies.—These studies showed little effect upon the incidence of pregnancy. The poor prognosis couples were slower in achieving pregnancy.

6. Length of Time From Completion of Survey to Time of Pregnancy.—Good prognosis couples achieved pregnancy sooner than did the poor prognosis couples. After two years, however, the percentage of couples with pregnancy was practically the same in both the good and poor prognosis groups.

7. Relation of Adoption to Pregnancy.—The number of pregnancies following adoption was not so high as might be expected if adoption were truly as good a "trigger" mechanism as is commonly assumed.

Dr. Buxton, we will return to the problems of infertility with which we have to work in our own clinic with the hope that we may in some small way contribute to the solution of some of the variables you have so clearly delineated.

DR. S. LEON ISRAEL, Philadelphia, Pa.—Dr. Buxton's thesis has emphasized for us that the experimental investigation of fundamental biologic factors in the physiology of reproduction, which so elevated animal husbandry, has not yet brought therapeutic success to the infertile couple. In such a couple, the dual task of selecting the principal cause of infertility and of evaluating the relative effectiveness of a given agent is difficult. The dilemma is heightened when the couple's case history is analyzed retrospectively, years later. Under such circumstances, personal bias creeps insensibly into conclusions, an error which can be eliminated only by the use of comparable and equal controls. Dr. Buxton has done this and, in so doing, has dramatized the fact that—without such controls—the clinician finds himself an enthusiastic exponent of one or another form of therapy for infertility. He has raised an interesting ghost. Seventy-two years ago, J. Matthews Duncan[1] wrote, "A reputation for curing sterility is spoken of as if it were founded on substantial claims. As in other departments of therapeutics there has been a great failure in logic: the *post hoc* and the *propter hoc* have been confused, a coincidence has been regarded as a consequence, and the credulity of patients and doctors alike has been the basis for useless and injurious practice."

It seems to me that in stating that all of his series had been sterile for at least one year, Dr. Buxton does not sufficiently underscore a major difference between couples whose infertility is of short duration and those whose problem is of long duration. The fact that his control groups are large, equaling his treated groups, does tend to give both kinds of couple equal representation. Despite this, my sense of the matter is that one must distinguish between sterility of short and of long duration for statistical purposes. For analysis of etiology, one year of infertility is sufficient to warrant complete investigation, entailing application of searching tests which Dr. Buxton has indicated are fairly rough rather than adequate. On the other hand, when one is evaluating treatment, it is far more accurate to consider only those couples infertile for two or more years. For such purpose, the most suitable controls would be untreated, *uninvestigated* couples. An infertile couple undergoing diagnostic survey is subjected to something we have not yet been able to evaluate properly. On another occasion, Dr. Buxton has himself put this point well by stating, "Pregnancy, as conclusive evidence of successful therapy in any sterility investigation, must be considered the result of the operation of known and unknown factors." An effect of investigation alone could be reduction of tension, that tension which results in chronic overproduction of endogenous epinephrine. In animals such a condition is accompanied by infertility, and its elimination by improved fertility.[2] How can we evaluate the salutary effect of the optimistic attitude of an enthusiastically investigated, not treated, patient?

Finally, Dr. Buxton has this morning closed the circle we have clinically run with therapeutic enthusiasm since the time that Duncan penned his critical words. I know of no better allusion with which to characterize our roundabout journey than this fragment from T. S. Eliot:[3]

> "And the end of all our exploring
> Will be to arrive where we started
> And know the place for the first time."

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DR. JOHN ROCK, Brookline, Mass.—I agree that a statistical analysis is quite impossible. One of the great difficulties is follow-up. Of course, the patients who became pregnant are the ones you know, so the balance is in their favor. Dr. Buxton has brought out that investigation alone frequently seems to result in pregnancy.

We try to establish the reproductive integrity of these couples but there are so many factors we cannot appraise, much less improve. What about the adhesions which cannot be felt and give no symptoms? How can we be sure of the incidence or duration of actual exposure to pregnancy? Nevertheless, this clinical condition of conceptual failure deserves as much attention as it is getting. The more we learn about reproductive physiology, the more we can help those who want to become pregnant and help, in a more acceptable way than is at present available, those who really do not want to and should not become pregnant.

DR. BUXTON (by invitation) (Closing).—I think Dr. Israel mentioned an interesting point in connection with a definition of sterility. This subject has been argued about for many years and gradually the conclusion has been reached that if a couple has attempted pregnancy for a year without success, they should be considered infertile. This is the present definition suggested by the American Society for the Study of Sterility. Possibly such a couple should not be considered infertile until after two years of unsuccessfully attempted pregnancy. Actually, from a practical point of view, I think their age makes a difference. When we see elderly sterility patients who have recently married and are anxious to have children, we are likely to institute investigation before we would in a younger couple.

PROBLEMS OF CELLULAR AND TISSUE DIFFERENTIATION IN PAPILLARY ADENOCARCINOMA OF THE OVARY*†

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THE term *differentiation* has been used by embryologists to describe the process by which specific organs and tissues are produced from a pre-existing embryonal matrix or anlage. The student of tumors has looked upon the genesis of neoplasms as, in a sense, the reversing of this process, as an abrupt or gradual loss of the recognized normal adult characteristics of tissues. In the most undifferentiated tumors, adult morphological structure and functional activity, as well as the ability to integrate with the other structures of the host, have disappeared and there remains only the capacity for self-nutrition and proliferation.

That carcinogenesis is the direct opposite of organogenesis, in the embryologic sense, cannot of course be maintained. Nevertheless, the loss of the ability to carry on specific function and the disappearance of the limitations upon growth or regeneration are the principal characteristics of neoplastic tissue. Since these biologic changes are paralleled by alteration in tissue structure it appeared possible to study by morphologic technique what we may call the degree of *differentiation of tumors.*

The differentiation of neoplasms or, more precisely, the degree of loss of differentiation, has already been the subject of some serious study. Certain classical contributions were made on this subject as much as fifty years ago[1, 5, 9, 10] and sporadic work on the grading of cancers has continued up to the present time.[6] Yet the significance of a varying degree of differentiation, as the essential phenomenon of new growth, seems not to have received full attention.[14]

Importance of Concept of Varying Degrees of Malignancy

Study of differentiation promises to be important from two aspects of the tumor problem:

A. Prognosis.—The relation of degree of differentiation to prognosis is the most obvious and the one to which attention has been devoted in the past. The recognition, by means of certain histologic criteria, of the line of division between what is benign and what is malignant is, of course, the chief responsibility of all tumor pathologists. The recognition of grades of malignancy more precise than that determined by this essential line is often attempted, but usually with indifferent success, since there are lacking clear criteria of successful grading, such as the obvious clinical signs or outcome which serve to prove the simple

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fact of malignancy. Varying degrees of malignancy, as they affect prognosis, are, however, tacitly accepted although they are regarded as of little practical value for the commoner types of cancer.[6, 8, 13]

B. Etiology.—The other relationship in which degree of differentiation may be significant is that of etiology. The generally held concept of carcinogenesis requires the investigator to study the circumstances under which a cancer may arise in a given tissue. With this approach cancer is looked upon as a homogeneous entity to be distinguished generically only from normal or benign tissue. Perhaps, however, the worker should be thinking of carcinogenesis not in terms of an event occurring in a single step but, instead, as a process consisting of a succession of stages of loss of differentiation. He would then no longer study *cancer, an entity,* but *malignancy, a quality,* regarded as present to a varying degree in different examples of tumors arising from the same tissue.

The present contribution is intended as an introduction to a research program based upon the latter concept. It must concern itself first with certain practical problems of grading, and in particular with the vital question of the consistency of grade. It will then proceed with a brief discussion of the program in general and with a single example given in detail of how such an approach has been utilized.

Practical Problems of Grading

The work being reported is based upon the adenocarcinomas of the ovary. This tumor was selected because past experience has shown that with it a fairly dependable relationship between clinical results and tissue structure can be demonstrated.[2, 7, 8, 13] In other words, these tumors have proved more "gradeable" than, for example, the epidermoid cancers of the cervix.

The criteria upon which tumors are graded may be divided into two groups, those concerned with characteristics of the cells themselves and those concerned with the relationship between cells. It appears probable that an ultimate system of grading will depend upon recognition of certain critical characteristics in the cell itself. For a beginning, however, we have depended on the more accepted and, with the conventional staining techniques, more evident differences notable in tissue structure resulting from the forms taken by cellular interrelationships.

When such microscopic tissue relationships are used as the basis of grading, it is important to remember that the form that tissue structure takes is dependent not only upon the inherent potentialities of the cells but also upon the indifferent tissues which they are invading. Neoplasms projecting freely into a cavity, such as that of the large bowel, of the endometrium, or of an ovarian cyst, have the opportunity to manifest their own growth characteristics, relatively unmodified by the effects of surrounding tissues. For these reasons, these tumors are the ones which can be graded with the most success, at least until cellular characteristics supersede tissue relationships as the basis of classification.

Characteristics Employed in the Grading of Ovarian Papillary Cystadenomas and Cystadenocarcinomas.—

The grading of even the papillary tumors of the ovary on the basis of general tissue relationships is far from a precise method. Nevertheless a series

of reports[8, 11, 12, 13] in the literature seem to indicate that there can be recognized, at least, benign tumors, those of doubtful or borderline histology, and several grades of malignant tumors. The distinguishing characteristics of these grades are as follows:

Benign Papillary Cystadenomas.—In the gross these are likely to appear as low, warty, intracystic excrescences. Microscopically examined, they are found to consist of broad papillomas, with much connective tissue covered by a single layer of low columnar epithelium.

Borderline Papillary Cystadenomas.—The histology of this type is best illustrated from the cases in which superficial peritoneal implantations have formed which have disappeared after the primary has been removed. Such cases have been described with photomicrographs in a former report.[12] The papillae of this type are much more complex, with fine branches, although blunt papillae with much connective tissue are also seen. The epithelium is now high columnar with cells closely packed, often with the appearance of growing in more than one layer.

Grade I. Papillary Cystadenocarcinoma.—The papillary structure is nearly everywhere maintained but a moderate multiplicity of cell layers is the rule. The cells are becoming larger and more rounded.

Grade II. Papillary Cystadenocarcinoma.—The papillae are now almost wholly epithelial with thin strands of connective tissue only. In places the crowding together of adjacent papillae gives the impression of solid masses of cells.

Grade III. Papillary Cystadenocarcinoma.—The tumor now gives the appearance of being a solid carcinoma, composed of sheets of cells. Difficulty may be encountered in finding areas in which the papillary structure can be identified. The cells are now round or polygonal with large nuclei, with little evidence of polarity to any basement membrane.

Problem of Consistency of Tumor Differentiation

If one is to utilize the apparent differences in the degree of malignancy in different tumors for the study of prognosis or etiology, one must be convinced that at least a considerable degree of consistency exists for each tumor. If the concept is to be useful in prognosis it is necessary that the tumor have the same malignant potentialities wherever it may be found in the primary tumor or indeed in the metastatic areas. For etiology it is important to know whether the tumor is relatively constant throughout its life history or is evolving from a benign or relatively differentiated tumor to one of higher malignancy.

Consistency With Regard to Time.—

To test the consistency of the degree of differentiation of the papillary tumors of the ovary with regard to time, the files of the pathology laboratory of the Department were reviewed and all cases in which there was a section from a late recurrence were selected for study. Fig. 1 illustrates the similarity of structure in tumor tissue taken from the same patient on two occasions separated by an interval of 13 years. Table I shows for 9 such cases a comparison of the

grade of the tumor at the original operation and at a subsequent procedure performed from ten months to thirteen years later. In 7 instances the structure was essentially identical, while in 2 there was a recorded variation of one grade.

TABLE I. COMPARION BETWEEN GRADE OF PRIMARY TUMOR AND OF RECURRENCE IN CASES OF PAPILLARY CYSTADENOCARCINOMA OF THE OVARY

CASE	HISTOLOGIC GRADE OF PRIMARY TUMOR	INTERVAL	HISTOLOGIC GRADE OF SECONDARY LESION	FOLLOW-UP AFTER SECOND OPERATION
1	Borderline	6 years	Borderline	Died 6 years
2	Grade I	13 months	Grade I	Died 13 months
3	Grade II	3 years	Grades II and III	Unknown
4	Borderline	8 years	Borderline	Died 8 years
5	Grade I	10 months 13 years	Grade I Grade I	Died 14 years*
6	Grade III with II areas	2 years	Grade II	Died 5 years
7	Grade I	5 years	Grade I	Died 7 years
8	Grade I (Pseudo-mucinous)	18 months	Benign (pseudo-mucinous)	Alive 21 years
9	Grade I	10 months	Grade I	Alive 19 years

*One year after second recurrence.

In a second group of cases the original operation, consisting of the removal of a single ovary, had been regarded as complete, but from eleven months to eleven years later a new or recurrent tumor had appeared in the preserved ovary. Fig. 2 again shows the similarity of structure exhibited by tissue removed from the same patient, this time with an interval of 5 years. Table II shows that in each of this series of 3 cases, the second tumor was identical in grade with the first. The late tumors, particularly Case 2, may have been simple recurrences of the first, and if this were true they should merely be added to the first group. If these were new tumors, however, they raise the interesting possibility of a predisposition of the organ of the host to tumors of a special grade.

TABLE II. COMPARISON BETWEEN GRADE OF FIRST PAPILLARY TUMOR AND OF SUBSEQUENT TUMOR IN OPPOSITE OVARY

CASE	HISTOLOGIC GRADE OF PRIMARY TUMOR	INTERVALS	HISTOLOGIC GRADE OF SECONDARY LESION	FOLLOW-UP AFTER SECOND OPERATION
1	Borderline	5 years	Borderline	Alive 6 years
2	Grade III	11 months	Grade III	Died 1½ years
3	Grade I	11 years	Grade I	Unknown

Parenthetically, it may be noted that consistency of differentiation has become a subject of interest to workers in the culture of human tumors in vitro and in animals. The so-called Hela strain, cultured several years ago from a case of human cervical cancer, is said to have maintained its fundamental characteristics to a remarkable degree in spite of passage through many subcultures and through animal hosts.[4]

Consistency With Regard to Area.—

In order to check the consistency with which one grade of malignancy is found throughout the extent of a given tumor at the time of the original operation, sections have been taken from multiple areas in a series of cases recently

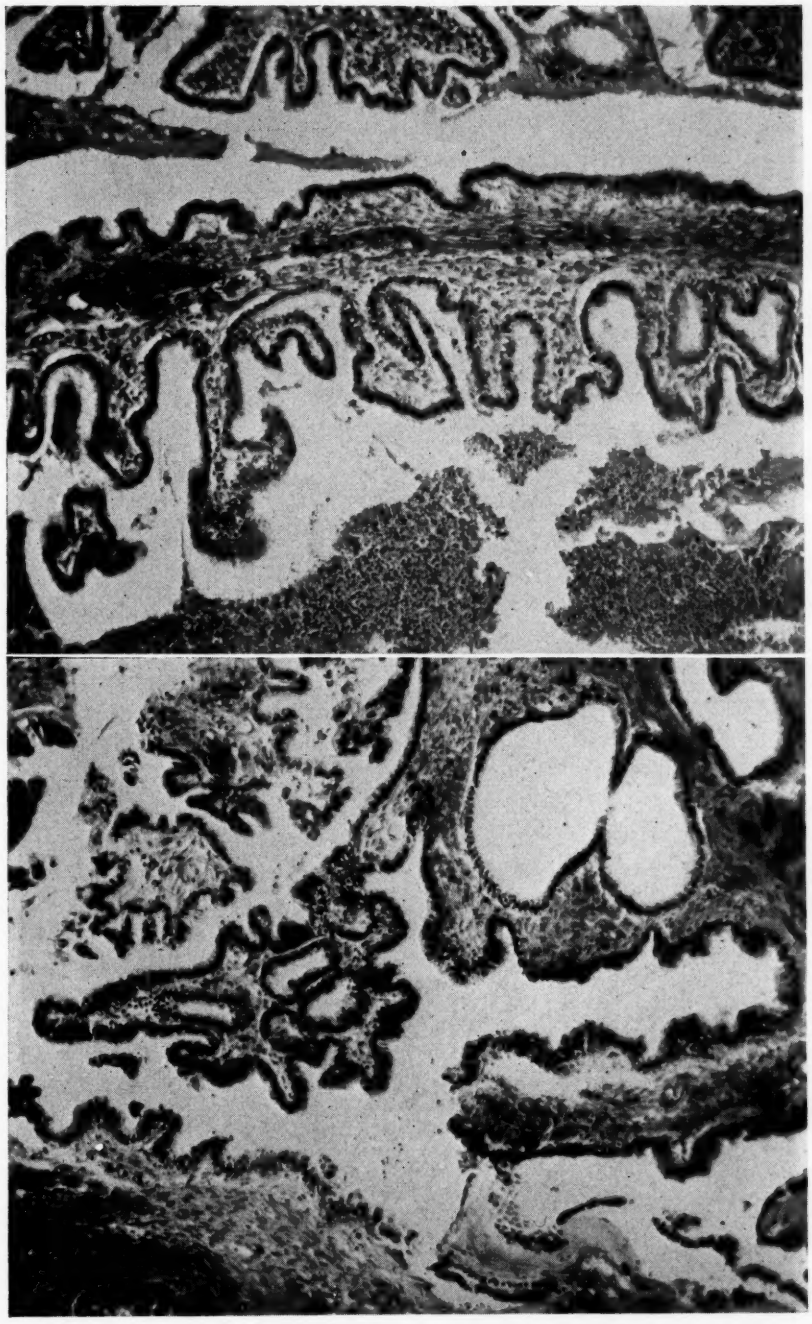

Fig. 1.—Comparison of structure of tumor at original operation (upper) and at time of recurrence 13 years later. Grade I. (×97.)

operated upon. Thirty-six papillary serous ovarian tumors have been so studied, 6 benign, 2 "borderline," and 28 malignant. From this group 550 sections have been taken from 215 areas to determine consistency of grading. Table III shows that only twenty-four sections of the 550 seemed inconsistent with the grade under which the tumor was classified.

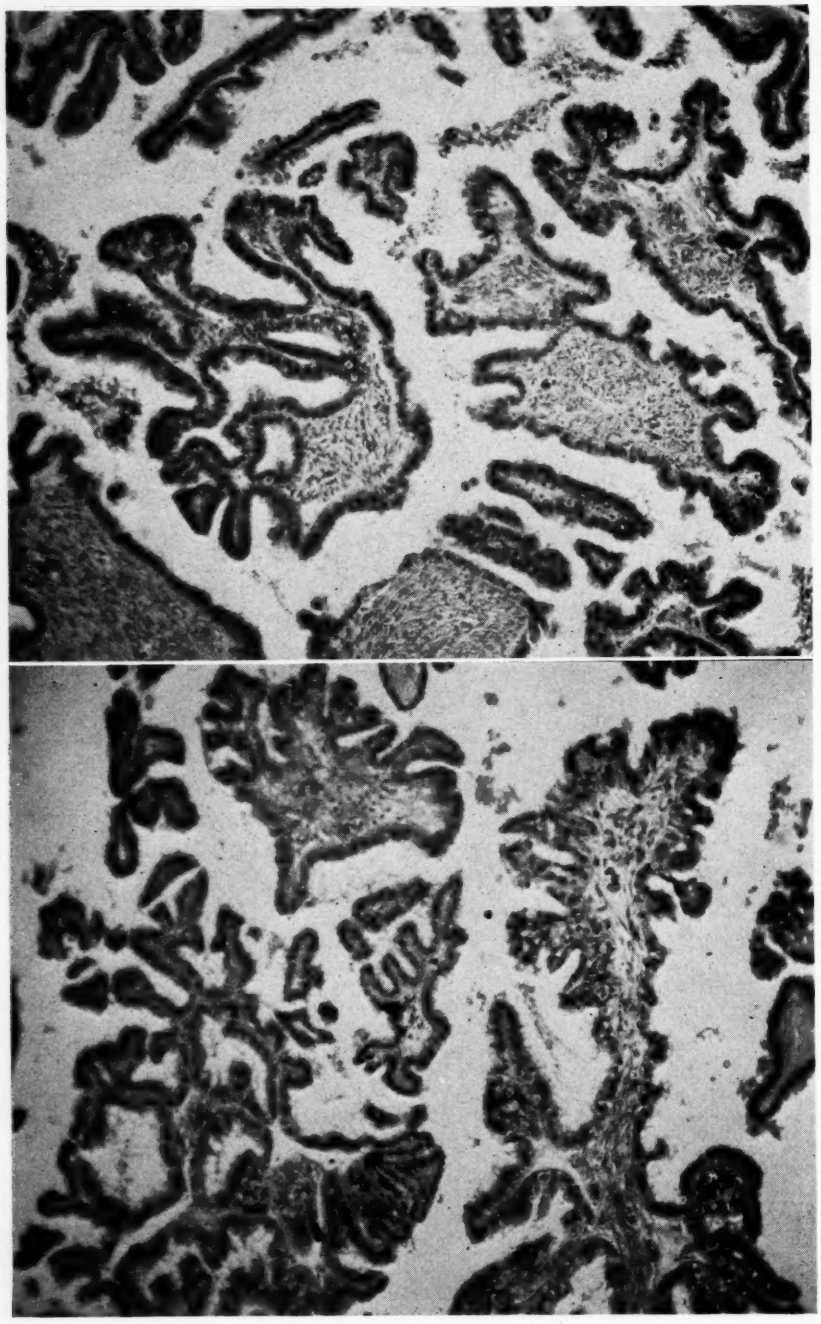

Fig. 2.—Comparison of structure of first tumor (upper) and of subsequent tumor in opposite ovary 5 years later. Borderline. (×97.)

TABLE III. CONSISTENCY OF GRADE IN DIFFERENT AREAS OF THE SAME TUMOR IN THIRTY-SIX CASES OF OVARIAN PAPILLARY SEROUS TUMORS

AVERAGE HISTOLOGIC GRADE	NO. OF CASES	TOTAL AREAS	TOTAL SECTIONS	SECTIONS BENIGN	SECTIONS BORDER-LINE	SECTIONS GRADE I	SECTIONS GRADE II	SECTIONS GRADE III
Benign	6	23	66	66				
Borderline	2	16	32	3	29			
Grade I	6	35	122			122		
Grade II	9	59	125				121	4
Grade III	13	82	205				17	188

It should be emphasized again that grading was established on the basis of areas in which the tumor tissue was growing freely and its structure affected as little as possible by defective blood supply, by adaptation to invaded connective tissue, or by crowding or necrosis. The relatively few inconsistencies recorded are perhaps due to the failure to take into consideration such local factors affecting tissue forms.

On the basis of this survey one may conclude that, in certain types of neoplasm at least, differences in degree of differentiation may be determined with some success, and that a single degree of differentiation is characteristic of that tumor throughout its extent and throughout at least long periods of its history.

A Plan for the Study of the Cytochemical and Biochemical Characteristics of Degrees of Malignancy

A search for biochemical or cytochemical characteristics which may vary according to the degree of differentiation seems therefore a logical approach to the study of the quality of malignancy itself. Possible limitations to such an approach appear indeed to be only technical, and whether progress can be made now or later seems dependent upon the availability of procedure rather than upon the logic of the approach.

TABLE IV. TYPES OF INVESTIGATION OF POSSIBLE USE IN CORRELATION OF QUALITIES OF MALIGNANCY WITH GRADE

I. Cytochemical Studies
   1. Ribonucleic acid (RNA)
   2. Desoxyribonucleic acid (DNA): absorption microspectrophotometry
   3. Nuclear proteins: histone and total
   4. Enzymes: alkaline and acid phosphatase, succinic dehydrogenase
   5. Glycogen

II. Biochemical Determinations
   1. Nucleic acids: RNA and nucleotides, DNA, RNA/DNA ratio
   2. Enzymes: d-amino acid oxidase, arginase, cytochrome oxidase, succinoxidase
   3. Soluble proteins: electrophoretic properties
   4. Glycogen content
   5. Metabolic studies: oxygen consumption under various conditions

III. Cellular Studies
   1. Tissue culture
   2. Cytology of living cells
   3. Cytochemical micrurgy

The original program set up three years ago envisaged a systematic screening of a number of measurable qualities of cells and tissues, these to be correlated with independently determined grades of malignancy. The work has been as complicated as had been anticipated.

All ovarian tumors are now collected in the operating room as soon as surgically removed and the tumor material distributed to several laboratories. If the amount of material in a given case is limited, it is apportioned to the several laboratories according to an accepted order of priority.

The primary classification is based on the clinical evidence of malignancy and a grade established by two persons studying multiple sections stained with hematoxylin and erythrosin. With the grade so determined, correlations are being sought between degree of differentiation and a number of qualities for the study of which techniques are available (Table IV).

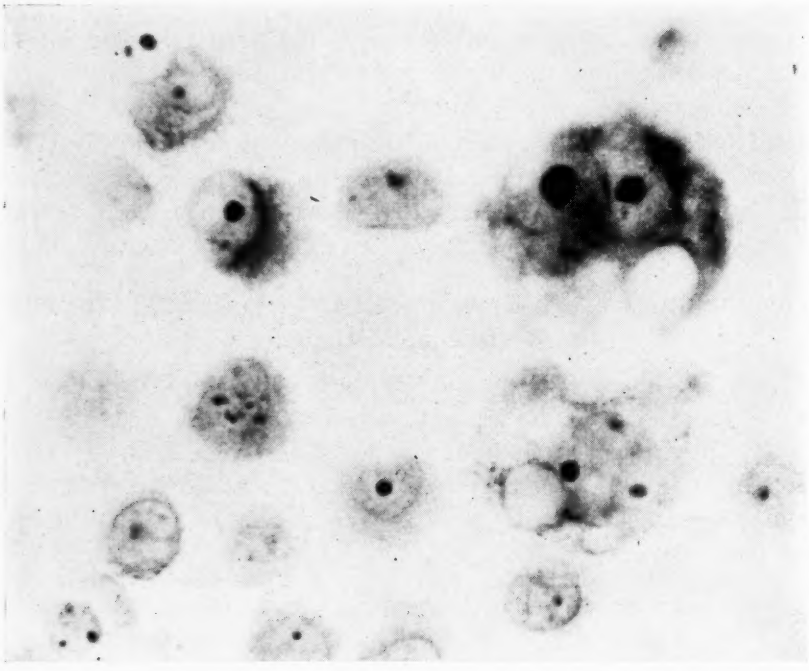

Fig. 3.—Cells from ascitic fluid showing variability in number and size of nucleoli in a Grade III tumor. Methyl green–pyronine Y. (×918.)

Cytochemical examinations are being made for ribonucleic acid (RNA), alkaline phosphatase, succinic dehydrogenase, and a few others. A new collaborator has recently begun the investigation of desoxyribonucleic acid (DNA) and nuclear proteins by the method of absorption spectophotometry.

Biochemically determinations are rendered difficult by the problem of separating cancer cells from connective tissues and the inconstant relationship which exists between the bulk of these two constituents of tumors. In spite of this difficulty, nucleic acid studies have been initiated on the RNA of nucleus and cytoplasm, on the DNA of the nucleus, on the rate of uptake of radioactive phosphorus, and on certain enzymes.

Metabolic studies of tissue respiration are in progress. These include determinations of oxygen consumption in air, in oxygen, with and without glucose and various other metabolites. The soluble proteins are being studied elec-

trophoretically. A number of quantitative studies are being done to determine the glycogen and lactic acid content of the tumor tissue.

Finally, material is being sent to Prof. M. J. Kopac in the Department of Biology at New York University, where correlated isolated cellular studies as indicated in Table IV are under way.

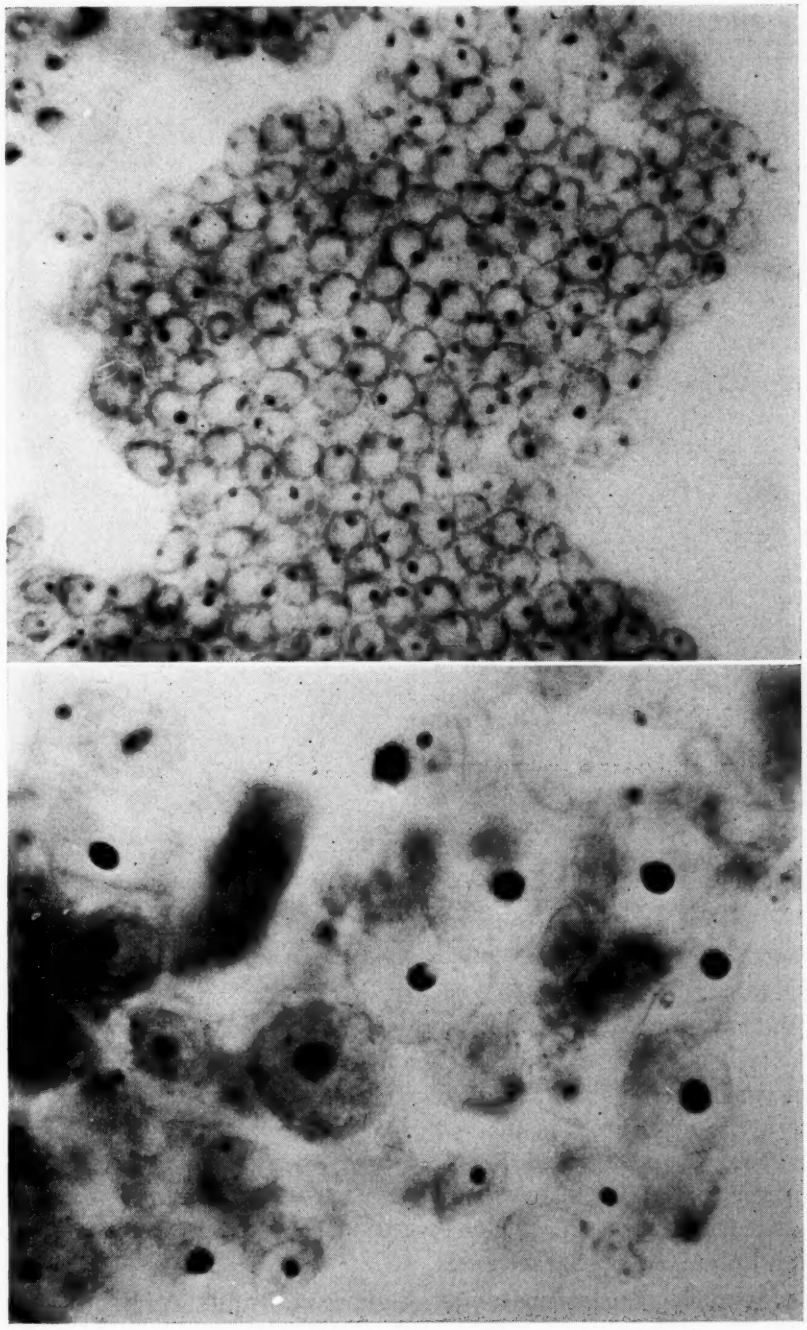

Fig. 4.—Cells from a tissue smear contrasting nucleoli in a borderline (upper) and Grade III tumor. Methyl green–pyronine Y. (×918.)

Results on most of this work will be available only over a period of several years. The purpose now is simply to report the plan of procedure and to give as an example a report of the study on the RNA of the nucleolus. Work on this led to results sooner than for the others, perhaps because of the simplicity of the procedure after its establishment, perhaps because, since only small amounts of material were needed, the case material accumulated more rapidly.

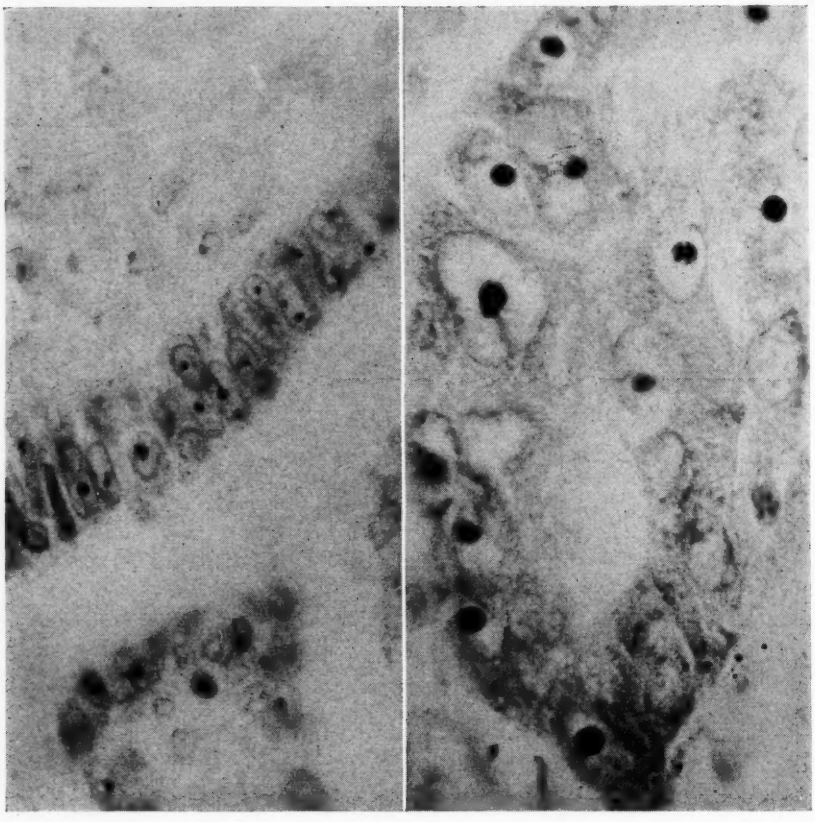

Fig. 5.—Tissue sections contrasting nucleoli in benign (left) and Grade III serous papillary ovarian tumors. Methyl green–pyronine Y. (×918.)

Cytochemical Studies of Ribonucleic Acid.—

Caspersson and his associate,[3] using ultra-violet spectrophotometry, have localized the two nucleic acids, DNA (desoxyribonucleic acid) in the chromatin and RNA (ribonucleic acid) in the nucleoli. In our work ribonucleic acid (RNA) in tissue sections and tissue smears has been investigated by utilization of the methyl green-pyronine method. With this method DNA is visualized as a blue-green substance and RNA as rose pink. The distinctive rose-pink reaction of nucleolar RNA makes it relatively easy to distinguish nucleolar bodies in resting nuclei. Fig. 3 shows a preparation made from the centrifuged sediment of fluid obtained by paracentesis.

In tumor nuclei, nucleoli occur as single or multiple structures. The number of nucleoli per nucleus and the average diameter of single nucleoli per nu-

cleus have been determined for 36 histologically graded human ovarian papillary serous tumors. An increase in the number of nucleoli as well as in their average size is fairly evident from a general inspection of these cases.

To illustrate this difference, Fig. 4 shows cells obtained from tissue smears from two tumors, one a borderline type, one a Grade III adenocarcinoma. The magnification is the same. A similar contrast is evident in the two tissue sections shown in Fig. 5, each again of identical magnification, the one at the left being benign, the one at the right a Grade III.

Number of Nucleoli.—Nucleolar counts per 200 nuclei in multiple areas of each histologically graded tumor indicate that the nuclei of benign tumors contain 1 to 4 nucleoli per nucleus and that with increasing grade of malignancy, the nuclei contain more nucleoli. In Grade III the numbers of nucleoli range from 1 to 24.

Table V presents an analysis of the percentage relationships of numbers of nucleoli per nucleus in the several grades. Although some nuclei in the first two groups may contain as many as 4 nucleoli per nucleus, borderline tumors have 4 times as many nuclei with 4 nucleoli as do benign tumors. In the graded malignant tumors with more than 5 nucleoli per nucleus, Grade III tumors contain a significantly higher number of nuclei with more than 5 nucleoli than do Grade I.

TABLE V. THE PERCENTAGE RELATIONSHIPS OF NUMBERS OF NUCLEOLI PER NUCLEUS TO THE DIFFERENT GRADES OF MALIGNANCY

HISTOLOGIC GRADE	NO. OF NUCLEOLI PER NUCLEUS			
	2	3	4	5+*
Benign	86.0	12.5	1.5	
Borderline	67.5	26.5	6.0	
Grade I	52.0	32.5	12.0	3.5
Grade II	41.0	27.0	19.0	13.0
Grade III	27.5	20.5	16.0	36.0

*Nuclei with more than 5 nucleoli per nucleus are reported in the 5+ column.

Size of Nucleoli.—Associated with increased numbers of nucleoli per nucleus with dedifferentiation is increased absolute size of single nucleoli as indicated by measurement of nucleolar diameters. Table VI presents the mean nucleolar diameter in nuclei with one nucleolus. Using nucleolar diameter as a criterion, it appears that single nucleoli per nucleus in Grade III tumor nuclei are almost three times as large as single nucleoli in benign tumor nuclei. These figures represent the mean of samples of the nucleolar population for each histologically graded group of tumors. Calculation of the standard deviation and

TABLE VI. MEAN NUCLEOLAR DIAMETERS OF SINGLE NUCLEOLI PER NUCLEUS IN THE DIFFERENT GRADES OF MALIGNANCY

HISTOLOGIC GRADE	MEAN (MM.)	SD	SE_m
Benign	.00131	.00011	.00005
Borderline	.00154	.00002	.00001
Grade I	.00149	.00025	.00011
Grade II	.00200	.00054	.00017
Grade III	.00297	.00043	.00015

of the standard error of the mean for each group shows that, within each group population, the range of measured mean diameters of single nucleoli is very small.

These data in regard to size and number of nucleoli, a measure probably of the amount of ribonucleic acid per nucleus, seem therefore to have a definite relationship to the degree of malignancy. It is one example of the type of correlation which, if others can be found, will produce a more precise knowledge of the nature of the malignant cell.

Summary

Loss of differentiation, or the grade of malignancy, has been discussed as one of the most significant characteristics of carcinoma and its study proposed as an important, and somewhat neglected, approach to cancer research.

An essential preliminary to a study of malignancy, based on such a concept, is the establishment of the consistency of tumor structure in any given case. It is believed that it has been shown that the degree of differentiation of at least the ovarian papillary serous tumors is, in fact, constant, not only as it appears in different areas of the specimen when surgically removed, but also during its natural life history as demonstrated by the structure of recurrences obtained several years after a primary operation.

Report is made also of the initiation of a program to determine certain cytochemical, biochemical, and biologic characteristics of malignancy by a search for measurable qualities that may be correlated with grade of malignancy. The number and size of the nucleoli, a measure probably of nucleolar ribonucleic acid, seem to bear such a direct relationship to grade of malignancy. The amount of nucleolar ribonucleic acid is an example of a characteristic which may be closely related to the quality of malignancy in ovarian tumors.

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Discussion

DR. R. R. GREENE, Chicago, Ill.—Dr. Taylor's presentation had to do with differences among benign, borderline, and malignant papillary tumors of the ovary. A stain was used which differentiates the two types of nuclear nucleic acids. These are desoxyribonucleic acid

or DNA, which is one of the main constituents of chromatin, which in turn is a main constituent of chromosomes. The amount of DNA in a given cell is correlated with, and dependent on, the number and size of chromosomes in that cell. In general there is no increase in the amount of DNA in tumor cells. Exceptions occur, however, when the number of chromosomes increases. The doubling or even quadrupling of the number of chromosomes may be fairly common in the cells of some tumors. The second or ribonucleic acid is the main constituent of the nucleolus or nucleoli. It is believed that the nucleolus is the main site of synthesis of nuclear and cytoplasmic proteins and that the nucleolus or the RNA is necessary for, or even controls, the rate of growth and division of cells. In rapidly growing cells one would expect an increase in the amount of RNA. Thus malignant cells should have and do have an increase of this substance with an associated increase in size and the number of nucleoli.

The fact that nucleoli are increased in size and number in malignant cells compared to normal cells has been known for a long time and has been used as one of the criteria for the diagnosis of malignancy. The present authors, however, have done more than contrast the nucleoli of malignant with those of normal cells. They have compared the nucleoli of benign, borderline, and varying grades of malignant papillary tumors of the ovary and have shown a significant increase in the number and in the size of the nucleoli with an increase in the malignancy of a tumor.

We have studied a smaller group of 18 papillary tumors of the ovary, using a methyl green–safranin stain worked out by Miss Milligan in our laboratory at Northwestern. With this technique, bright red nucleoli stand out and are sharply demarcated from chromatin particles which stain poorly, if at all. Our findings were not subjected to detailed tabulations and analysis. In 3 poorly differentiated carcinomas, the nucleoli were extremely large and numerous. This was also true in one moderately differentiated tumor. In two other moderately differentiated tumors the nucleoli were moderately increased in size and in number. In two well-differentiated tumors the nuceloli were not increased in size and number. These were, however, papillary pseudomucinous cystadenocarcinomas, and I do not know if they vary in this regard from the more common serous type. Five papillary tumors were judged to be of the borderline type. The nucleoli were slightly increased in one and normal in 4. Interestingly enough, one of these latter had metastases to the omentum at the time of operation. Dr. Gardner tells me the patient is alive and well seventeen years later. Finally, five were considered to be benign. The nucleoli were slightly increased in one and normal in the others. As can be noted, the findings in so far as nucleoli are concerned were the same in the benign and in the borderline group. This is not surprising as the histologic distinction between the two is obscure and with me, at least, seems to vary from day to day. As is obvious, our findings agree very well with those of the authors.

DR. TAYLOR (Closing).—We have worked on this project now for three years. We have found one measurable factor which seems to correlate more or less well with the degree of malignancy and are now looking for others. The techniques which are carried out by specialized laboratory investigators are extremely difficult, and I do not know when, if ever, another factor may be reported which seems to be as closely related to the degree of malignancy as does the ribonucleic acid of the nucleolus.

THE REASONS FOR DECREASED HISTIDINE EXCRETION IN PRE-ECLAMPSIA*†

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THE increased urinary excretion of histidine and certain other amino acids in normal pregnancy has been recognized for thirty years, and has been amply confirmed by colorimetric, chromatographic, and microbiological analyses. The nonpregnant individual excretes an average of 175 mg. of free histidine daily[1, 2] whereas a woman 5 to 8 months pregnant excretes from 300 to 900 mg. per day.[3] We have recently demonstrated[4] that there are three distinct causes for this increased histidinuria of pregnancy: (1) a marked increase in the rate of glomerular filtration, (2) a reduction in the rate of renal tubular reabsorption of histidine, and (3) a significant reduction in the rate at which histidine enters the intracellular compartment of the body. For most pregnant subjects the first of these three is, quantitatively speaking, the most important.

In 1941, Kapeller-Adler[5] found very low values for histidine excretion in pre-eclampsia, an observation which has been repeatedly confirmed.[6-9] She postulated that glomerular damage prevented the filtration of histidine, and that some of the amino acid was converted to histamine. Beyond these suggestions, there have been no serious attempts to explain the reduced amino aciduria of pre-eclampsia.

The Possible Causes for Reduced Histidine Excretion in Pre-eclampsia

The following list would appear to exhaust all of the possible mechanisms by which the histidinuria of normal pregnancy could be reduced in the presence of pre-eclampsia:

1. A decreased rate of glomerular filtration
   (a) due to a decreased filtration of water or
   (b) to a glomerular "block" for histidine.
2. Increased renal tubular reabsorption of histidine.
3. A reduced rate of histidine absorption by the gastrointestinal tract.
4. Low plasma levels of histidine
   (a) due to more rapid metabolism or
   (b) to a conversion to histamine.

Each of these possibilities will be examined in the present study.

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†Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24 and 25, 1955.

Methods

Nine subjects with pre-eclampsia of varying severity were selected for study. Table I indicates the week of pregnancy, the clinical diagnosis, the blood pressure, and the degree of proteinuria existing on the day of the experiment. (In all graphs illustrating data, the subjects are arranged in the same order as shown in Table I.) Each subject was restudied by the same techniques several weeks post partum, thus serving as her own control.

TABLE I

CASE NO.	WEEK OF PREGNANCY	CLINICAL DIAGNOSIS	ON DAY OF TEST	
			B. P.	PROTEINURIA
1	38	Pre-eclampsia, moderate	140/90	2+
2	30	Pre-eclampsia, severe	145/95	4+
3	36	Pre-eclampsia, mild	125/80	1+
4	37	Pre-eclampsia, severe	175/110	3+
5	25	"Recurrent toxemia," mild	120/85	2+
6	36	Chronic hypertension Superimposed pre-eclampsia	165/115	4+
7	40	Pre-eclampsia, severe	160/105	3+
8	37	Pre-eclampsia, severe	170/120	4+
9	27	Pre-eclampsia, moderate	155. 110	1+

The methods employed were identical with those which we described in 1954.[4] Priming doses of inulin and L-histidine were given intravenously, followed by infusion at a constant rate of both substances. After the period of equilibration, blood and urine samples were collected for three consecutive clearance periods of twenty minutes each. Inulin was determined by the method of Roe, Epstein, and Goldstein.[10] Plasma and urinary levels of histidine were determined microbiologically using *Leuconostoc mesenteroides* as the test organism. The mean value for the three clearance periods was corrected to 1.73 sq. M. of body surface using the body weight on the day of the test.

The gastrointestinal absorption of histidine was studied in four additional subjects with pre-eclampsia, and the urinary excretion of D-histidine and L-histidine was compared in 3 patients with toxemia. Colorimetric procedures previously described[3, 11] were employed for these experiments.

Results

Histidine Clearance.—The mean rate at which plasma was cleared of histidine during pre-eclampsia was 7 ml. per minute. This was not significantly lower than the mean postpartum rate of 11 ml. per minute found in the same group of subjects (Fig. 1). In fact, 3 women had higher clearance values during the toxemia than they did after delivery.

The clearance of plasma histidine in pre-eclampsia was markedly lower than that observed in a normal gestation of about the same duration. The mean clearance in 12 subjects with normal pregnancies was 25 ml. per minute. Thus the reduction of histidinuria in pre-eclampsia was confirmed. Histidine has often been reported "absent" in the urine of women with toxemias, but this is only because the amount present is below the sensitivity threshold of certain colorimetric methods. It is probably always present when measured by the microbiologic technique.

Glomerular Filtration Rates.—In all but one case, the inulin clearance was actually lower during pregnancy than it was several weeks after delivery (Fig. 2). The exception (Case 6) had essential arteriolar hypertension plus

pre-eclampsia, and both the antepartum and postpartum values were low. The mean filtration rate during pre-eclampsia (75 ml./min. ± 18) was not only significantly lower than the level after delivery of 109 ml./min. ± 19 for the same subjects, but was in striking contrast to the high rate of inulin clearance observed in normal pregnancy (181 ml./min. ± 33).

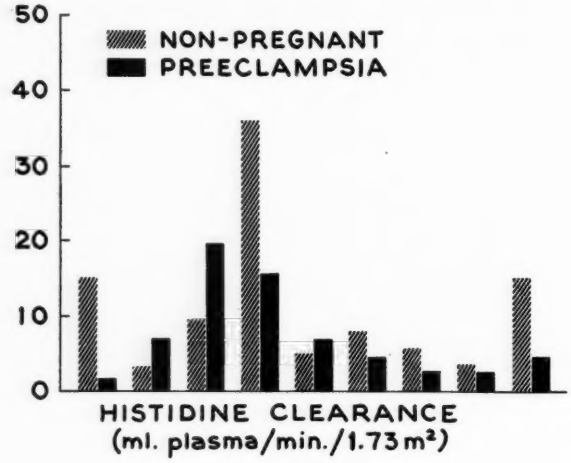


Fig. 1.

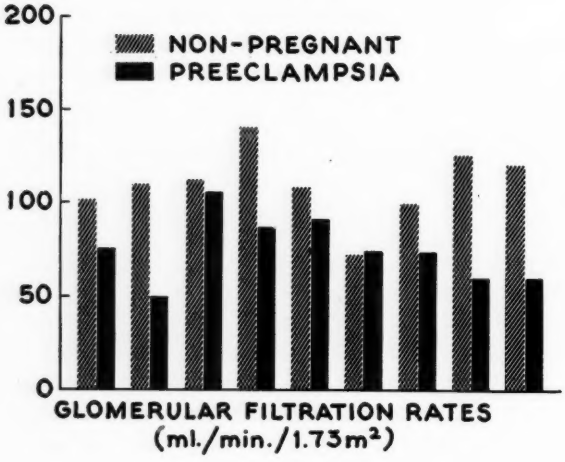


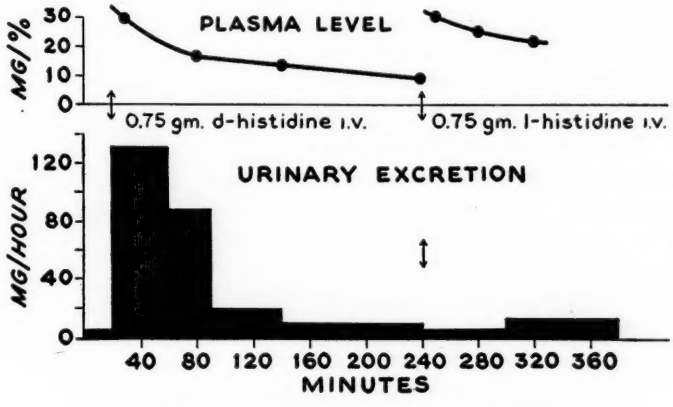
Fig. 2.

Thus the rate of glomerular filtration in the 9 subjects studied was only 42 per cent of that we had previously determined for normal pregnancy of 30 to 38 weeks' duration.

The Question of a Glomerular "Block" for Histidine.—On a priori grounds, it would be difficult to believe that histidine could be "held back" by damaged glomeruli to any greater extent than the larger molecule, inulin. Nevertheless, since this has been claimed,[6, 9] we restudied some unpublished data that one of us (E. W. P.) obtained in 1946 on 3 patients with severe pre-eclampsia. In this study, the urinary excretion of the unnatural isomer D-histidine was compared with L-histidine following the intravenous injection of each amino acid. Fig. 3 is typical of the results obtained in all 3 subjects.

There was no apparent renal rentention of D-histidine because this compound is poorly reabsorbed by the renal tubules. The excretion of L-histidine,

normally well reabsorbed by the tubules, was not increased following injection. It would be strange indeed if glomerular capillaries could distinguish between optical isomers of the same amino acid.



COMPARISON OF D. vs. L.-HISTIDINE IN PREECLAMPSIA

Fig. 3.

Fig. 4.

The Renal Tubular Reabsorption of Histidine.—In normal pregnancy, as compared to the nonpregnant state, the percentage of histidine reabsorbed by the renal tubules is consistently reduced.[4] In pre-eclampsia, there is no consistent change in this function when compared to the nonpregnant status of the same individual (Fig. 4). The mean percentage of filtered histidine which was excreted (i.e., escaped tubular reabsorption) during pre-eclampsia was 9 per cent, essentially the same as the values in the nonpregnant state of 9 to 11 per cent. It was, however, significantly lower than the 17 per cent tubular rejection found in normal pregnancy, and this fact contributed to the reduced histidinuria noted in pre-eclampsia. Quantitatively speaking, however, the change in the tubular reabsorption rate was not quite so important as the reduction in the filtered load delivered to the tubules.

The Gastrointestinal Factor.—In the present experiments, all histidine was administered intravenously, thus by-passing the gastrointestinal tract. The

fact that under these circumstances reductions of histidine clearance were still noted in pre-eclampsia would tend to eliminate variations of intestinal absorption as a major factor.

The blood levels of histidine achieved after the oral ingestion of 3.0 Gm. of L-histidine were much lower in normal pregnancy than they were in nonpregnant women.[11] In pre-eclampsia, however, the same methods of study revealed higher blood levels achieved more rapidly. This would tend to increase, rather than decrease, the rate of histidinuria in toxemia. Thus the gastrointestinal tract may be dismissed as a factor contributing to the reduced histidine excretion in pre-eclampsia.

The Metabolism of Histidine in Pre-eclampsia.—The derivation of a formula for estimating the rate at which infused histidine entered the intracellular compartment of the body has been described in our previous publication.[4] The calculated value for M is literally the number of grams of histidine per hour which is not excreted by the kidneys but leaves that space in the body currently occupied by inulin. In the 9 cases of pre-eclampsia under study, the value for M was 0.89 ± 0.09 Gm. per hour. This is significantly lower than the value in the nonpregnant state of 1.02 ± 0.09 Gm. per hour for the same subjects. It is intermediate between the value of M for normal pregnancy (0.81 ± 0.15 Gm./hr.) and that for the nonpregnant status.

These calculations indicate that the factors responsible for the decreased rate of extrarenal loss of histidine in normal pregnancy are still operating (though perhaps to a lesser degree) in pre-eclampsia. Obviously this would tend to increase histidinuria; so alterations of histidine metabolism cannot account for the observed changes in toxemia.

In 1941, Kapeller-Adler[12] suggested that in severe toxemia histidine, instead of being excreted as such, was transformed into histamine, which she found in small quantities in the urine of toxemic patients. There are at least three findings which oppose this view: First of all, the more rapid conversion of histidine to any of its possible metabolites should result in reduced blood levels. The fasting plasma level in pre-eclamptic subjects (mean = 1.8 mg. per 100 ml.) was actually higher than that for normal pregnancy (mean = 1.6 mg. per 100 ml.). Second, Rockenschaub[13] has recently found that the urinary excretion of histamine falls to very low levels in pre-eclampsia. Third, it is obvious that if any significant proportion of the histidine which we administered intravenously to pre-eclamptic subjects were rapidly converted to histamine, some obvious clinical disaster should have ensued.

Comment

The essential statistical data relative to histidinuria in normal pregnancy and in pre-eclampsia are presented in Table II. It can be seen that the filtered load of water and of histidine delivered to the renal tubules is only 42 per cent of that which is characteristic of normal pregnancy. Furthermore, almost twice as much of this filtered load escapes tubular reabsorption in normal pregnancy as in pre-eclampsia. These two factors alone combine to cause the reduced excretion of histidine in this disease.

The marked decrease of inulin clearance in pre-eclampsia *as compared with normal pregnancy prior to term* was noted by Vara and Vehniäinen,[14] and has been confirmed by Bucht,[15] Bonsnes,[16] de Alvarez and Richards,[17] and in this study. This may be one of the most important physiologic changes in true pre-eclampsia. The increased glomerular filtration rate of normal gesta-

tion appears to be related to the curve of expanded plasma volume and cardiac output, whereas the decrease in pre-eclampsia must be related to a constriction of the afferent glomerular arterioles. In other words, normal pregnancy is characterized by a new glomerulotubular balance which is disturbed in pre-eclampsia. The disturbance of this balance could account for the reduced excretion of sodium and water, as well as amino acids and other metabolites.

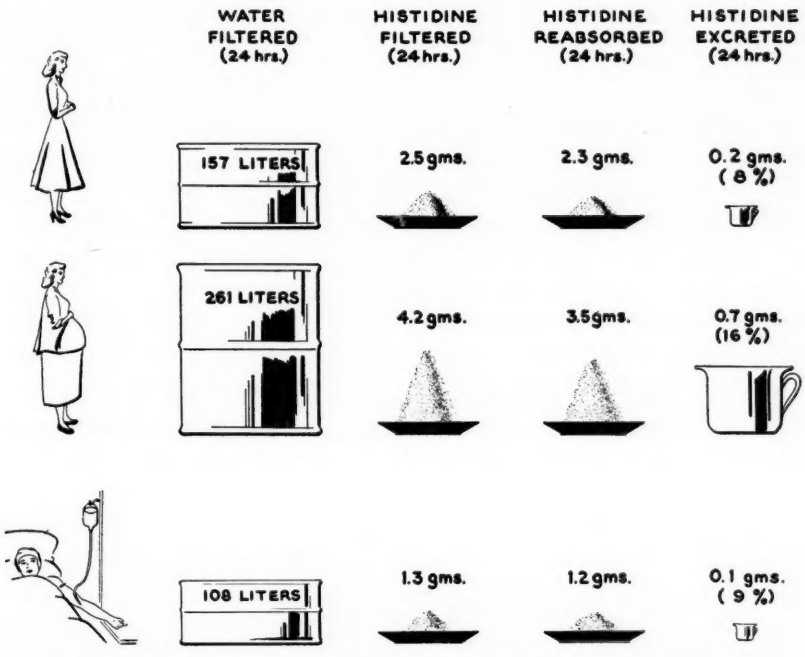


Fig. 5.—The renal transport of histidine in normal nonpregnant women, normal pregnant women, and pre-eclamptic subjects, respectively. The mean values, corrected to a body surface of 1.73 sq. M., are for fasting subjects prior to the administration of histidine.

In 1950, Stephens and associates[18] noted an increased histidine excretion in patients being treated with cortisone and ACTH. In a study designed to explain this finding, Grob[19] found that ACTH or cortisone caused a considerable decrease in the tubular reabsorption of histidine (from 92 to 79 per cent). He also found that the extrarenal uptake of histidine from the extracellular fluid (referred to as the M value in our studies) was reduced by 17, 33, and 50 per cent, respectively, in the 3 patients studied. These changes are qualitatively the same, though greater in extent, than those we observed in normal pregnancy. This strongly suggests, as Grob pointed out, that the renal tubular and metabolic changes affecting histidine in normal pregnancy are brought about by the increased production of "corticoids."[20] The same hormonal factors must be operating, but to a lesser degree, in pre-eclampsia.

This reduction in the rate of metabolism for histidine does not apply to all amino acids. We have calculated the M values for glycine and found them to be identical for the pregnant and nonpregnant states.

A graphic portrayal of the renal transport of histidine during the fasting state is presented in Fig. 5.

TABLE II*

	(1) G. F. R.	(2) HISTIDINE CLEARANCE	(3) RENAL TUBULAR REJECTION	(4) METABOLISM
Normal Subjects.—				
Pregnant	181 ± 33	25 ± 13	17% ± 7	0.81 ± 0.15
Not pregnant	109 ± 16	9 ± 6	8% ± 4	1.02 ± 0.04
Significance of difference	< 0.01	< 0.01	< 0.01	< 0.01
Toxemia Subjects.—				
Pregnant	75 ± 18	7 ± 6	9% ± 6	0.89 ± 0.09
Not pregnant	109 ± 19	11 ± 10	10% ± 7	1.02 ± 0.09
Significance of difference	< 0.01	None	None	< 0.02

*This table shows the means and their standard deviations for 12 normal pregnancy subjects and 9 subjects with pre-eclampsia. Column (1) gives the glomerular filtration rate in milliliters per minute. Column (2) gives the milliliters of plasma cleared of histidine by the kidneys each minute. Column (3) shows the per cent of filtered histidine which escaped tubular reabsorption. Column (4) gives the number of grams of histidine which presumably entered the intracellular compartment of the body each minute during the infusion. All values are corrected to 1.73 sq. M. of body surface.

The figure for significance is the probability of chance occurrence (p). Values exceeding 0.05 were not considered to be of significance.

Summary

Nine subjects with pre-eclampsia were given constant-rate infusions of inulin and L-histidine for the purpose of studying the renal transport of histidine. Identical studies were repeated on the same subjects several weeks after delivery. The amino acid was assayed microbiologically in all but a few additional experiments designed to compare the excretion rates of D- and L-histidine and the gastrointestinal uptake.

The histidine excretion rate and plasma clearance were invariably lower in pre-eclampsia than in normal pregnancy. Two factors combined to produce this effect: (1) a marked diminution in the rate of glomerular filtration (inulin clearance) and (2) an increased rate of tubular reabsorption when compared with the normal pregnancy rate.

The rate at which histidine entered the intracellular compartment of the body during pre-eclampsia was significantly lower than the rate in the nonpregnant state but somewhat higher than that for normal pregnancy. This factor would tend to increase histidinuria above nonpregnant rates, but was counterbalanced by the depressed glomerular filtration.

No evidence was found for (1) a reduced rate of gastrointestinal transport for histidine, (2) a glomerular "block" for histidine, or (3) any appreciable conversion of histidine to histamine.

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Discussion

DR. ALLAN C. BARNES, Cleveland, Ohio.—Dr. Page extends previous studies by reporting investigations on the *declining* urinary output of histidine in the patient with pre-eclamptic toxemia. In considering his findings, one has a rather obvious choice between the hypothesis that these renal changes affect all amino acids indiscriminately, or that histidine is completely unique in its metabolism in the obstetric patient. The first of these—that all amino acids behave in this same fashion—can be quickly shown to be untenable. Thus, as Dr. Page mentions, glycine does not behave in this manner at all. Other workers have shown that leucine, isoleucine, and methionine, for examples, demonstrate a change in pregnancy which is scarcely significant statistically. Tryptophane administered to the pregnant woman leads to the excretion of the abnormal metabolite xanthurenic acid. Tyrosine shows a sharp increase in excretion during pregnancy, although its excretion rate in the toxemic patient is not known. There is no consistent pattern of behavior which would suggest that these renal changes affect all amino acids equally.

On the other hand, as has been pointed out by others, the histidine changes are the most pronounced and striking. Of all the amino acids it is the only one with no overlap —the highest nonpregnant levels are always below the lowest levels in pregnancy. We are apparently left with the thesis that the metabolism of histidine in normal and toxic pregnancies is a unique phenomenon, and while Dr. Page's excellent study explains *what* causes the observed changes in the toxemic patient's histidine excretion, the question still intrigues one as to *why* histidine should behave so differently from the other amino acids.

The rise in glomerular filtration rate in normal pregnancy and its fall in the pre-eclamptic toxemias are changes that have been recognized for several years. Presumably these changes by themselves would first increase and, in toxemia, decrease the elimination of all the amino acids by approximately the same amount. So that one must look further than the alterations in glomerular filtration rate to explain the unique behavior of histidine.

Several potential explanations immediately come to mind, of course. The calculations of tubular reabsorption which Dr. Page has made for histidine have not been carried out for other amino acids, and a selective tubular absorption might account for this phenomenon. It is generally recognized that the glomerular filtration rate, on the one hand, and tubular reabsorption, on the other, function under totally separate control mechanisms and do not necessarily move in the same direction. Parenthetically we might note with respect to sodium that the falling glomerular filtration rate combined with a continuing high reabsorption rate by the tubules could account for the entire phenomenon of sodium retention in our toxemic patients.

We should also note that histidine has a unique chemistry, being the only essential amino acid possessing an imidazole ring in its nucleus. Or there might be a difference in the placental handling of histidine, a topic as yet not investigated. Finally, there is the enchanting concept that this is a reflection of fetal growth. Histidine's indispensability as an essential amino acid is for growth; it is not one of the group essential for the maintenance of nitrogen equilibrium. In the presence of an actively growing baby this amino acid appears in increased amounts, but the baby of the toxemic mother does not grow as actively as the baby of the nontoxemic woman, and this is the very time when the histidinuria declines. In MacDonald House the average weight of babies of toxemic mothers is 2,592 grams, whereas the average weight of the babies of a control, nontoxic group of mothers of the same duration of gestation is 3,157 grams. These figures parallel the rise and fall of this growth-essential amino acid in the maternal urine.

LONGEVITY FOLLOWING PELVIC EXENTERATION FOR CARCINOMA OF THE CERVIX*

LANGDON PARSONS, M.D., AND MELVIN TAYMOR, M.D., BOSTON, MASS.

BRUNSCHWIG[1] first reported his experience with ultraradical surgery for advanced or recurrent malignant disease in the pelvis in 1948. Since that time there has been considerable interest in the so-called pelvic exenteration procedure. It has been both favorably received and much maligned. One may reasonably question how radical we should be in dealing with advanced malignant disease.

Following Brunschwig's experience a series of cases of advanced or recurrent malignant disease of the pelvic organs was initiated. The first operation was performed in December, 1947. Since that time 116 have been done. At the outset we were interested in attempting to find out: (1) if the patient could survive surgery of this magnitude, (2) whether she could be restored to a useful life and be happy in her new existence, and finally (3) whether there could be any long-time salvage.

The initial experience with the cases in this series was reported in 1950.[2] Indications, rationale technique of operation, pre- and postoperative care were discussed in that communication.

Sufficient time has now elapsed and enough operations have been performed to convince us that patients can survive extensive surgery of this type and continue to live useful and happy lives. This report considers the trend in longevity.

In a recent communication Brunschwig[3] reports the survival rates in 315 cases of pelvic exenteration, for all types of advanced pelvic cancer. The five-year survival figure of 12 per cent is commendable, particularly where comparison is made with the salvage to be expected from operations for advanced carcinoma of the lung, pancreas, stomach, or esophagus.

In addition to the large number of cases of advanced or recurrent carcinoma of the cervix, the operation was also performed on many cancers arising in endometrium, ovary, sigmoid, and rectum, as well as vagina and vulva. Indeed, some males were included in this report. No attempt was made to discuss the pelvic exenteration procedure in relation to malignant disease in any single location.

We have elected to confine our observations on longevity following the pelvic exenteration procedure to cancer of the cervix alone. Eighty-six such operations have been performed for advanced or recurrent carcinoma of the cervix over an eight and one-half year period.

In the same period of time 30 operations have been done for cancer of the endometrium, ovary, and rectum. Two of these were uterine sarcomas. Only

*Presented, by invitation, at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

one of this group lived longer than two years. The operative mortality figures were appreciably higher. It is our growing conviction that the pelvic exenteration should be reserved for patients with cancer of the cervix whose life history gives fair assurance that the disease is confined to the pelvis. Cancer of the vulva, vagina, and urethra would be in the same category.

Selection of Cases

Initially the pelvic exenteration was offered only to patients who had recurrent disease after either radiation or the Wertheim type of hysterectomy.

Recurrence after irradiation in the form of radium, x-ray treatment, or both was the indication for pelvic exenteration in 70 per cent of the cases in this series (Table I). Fifty-three per cent had extensive damage to one or both kidneys noted in the preoperative evaluation. In our experience reradiation of a patient who has failed to respond satisfactorily to adequate therapy on the initial attempt produces only discomfort without increasing longevity.

TABLE I. INDICATIONS FOR PELVIC EXENTERATION IN 86 CASES OF CARCINOMA OF THE CERVIX

	NO.	PER CENT
Radiation recurrence*	60	70
Primary Stage III or IV	21	24
Recurrence after Wertheim	5	6

*Three cases showed only radiation necrosis in specimen.

To make an accurate appraisal of what can be accomplished by this operation one must keep in mind that the majority of these patients were offered operation only after known forms of conservative therapy had been exhausted. Many of these patients had truly been given up for lost.

When it became evident that patients in this unfavorable group could survive the operation and return to a normal, happy existence, the indications were broadened. The operation is now considered as primary treatment for patients who have such extensive disease that treatment by standard forms of therapy offers small chance of survival. Twenty-one patients with tumors classified as Stage III or IV when first seen were offered pelvic exenteration as the primary treatment. The disease had involved bladder, rectum, or pelvic peritoneum. Standard methods of therapy can offer less than 5 per cent five-year cures in this group.

Eleven of the 21 had large tumors with preoperative or postoperative evidence of bladder involvement, yet failed to have these observations confirmed on subsequent pathological examination. Since staging or the extent of the disease is based on clinical evidence, these 11 cases must remain in Stage IV. All who deal with this type of case have commented on the difficulty of evaluating the extent of the disease. The impression of the frozen pelvis noted on bimanual palpation, even under anesthesia, frequently is not substantiated when abdominal exploration is performed.

As further evidence of the difficulty in estimating the extent of the disease following radiation, three patients presented firm pelvic masses located in such a position that satisfactory biopsies could not be obtained without removing the tumor. The pathologist reported extreme radiation necrosis without active tumor. Experience has shown, however, that on occasion the initial report of radiation necrosis had to be changed when multiple sections revealed scattered foci of carcinoma. One of the 3 patients subsequently died from pulmonary metastases.

Five patients with cervical carcinoma were subjected to the exenteration operation when recurrence appeared after a Wertheim hysterectomy. Partial exenterations (the rectum spared) have been done as an extension of the Wertheim hysterectomy in certain cases where either preoperative evidence or abdominal exploration indicate encroachment on the bladder by tumor.

The Operation

The complete or total pelvic exenteration consists of a block dissection of the contents of the pelvis, including the uterus, tubes, ovaries, vagina, bladder, rectum, vulva, and the pelvic lymph nodes. Diversion of the urinary stream is achieved by transplanting the ureters either into a colostomy loop or bringing them to the skin as ureterostomies. This procedure was carried out in 64 of the 86 cases.

The details of the operation have recently been recorded.[4] Major modifications in technique from that of the original report[2] have to do with isolation of bowel segments and the mechanics of ureterosigmoid anastomoses. In the earlier cases, a perineal stage of the operation, removing the specimen from below en bloc with the vulva, was invariably performed. The operation is now done entirely through the abdomen. The specimen includes the entire vulva. This modification was suggested by Meigs and Ulfelder.[5]

With the increasing experience we have come to have little brief for the operation as a palliative procedure. Ideally one should carry out this form of selection preoperatively but we are convinced that operability can be determined only by explorations. The operations are deliberately planned, however, so that if extensive dissection indicates that complete eradication of the disease is not possible, the surgeon may abandon the procedure before permanent damage to ureter, bladder, or rectum has occurred. This approach carries with it an increased risk. In many instances this is not feasible, for the surgeon frequently commits himself so far that there is no other recourse than completion of the operation. The emphasis is on cure, not palliation.

In 22 cases the malignant disease was confined to the region of the bladder and a partial exenteration was carried out, removing the bladder but preserving the rectum. It may be argued that this operation is incomplete. Brunschwig, Ulfelder, and Meigs have noted a high incidence of recurrence and reported poor results from this type of procedure.

Believing that the reason for the high incidence of recurrent disease reported from this operation lies in the failure to remove disease dormant in the lymphatics which course dorsally close to the rectum, we have made it our practice to dissect the rectum cleanly, removing all pararectal tissue from all sides of the rectum. At the end of the procedure a 6 to 8 inch length of rectum lies completely free in the pelvis, deriving its blood supply from the superior hemorrhoidal vessels above. To date we have encountered no instance of necrosis due to inadequate blood supply. Function of the bowel has not been disturbed and rectal continence has been preserved.

The method of dealing with the ureters has undergone a revision with the passage of time. In the early experience sigmoid anastomoses were carried out by merely passing a ureter through a small 1 cm. opening in the bowel and securing the fish-mouthed ends with a single mattress suture. The end results were unpredictable. Some of the patients made an uneventful convalescence. Many, however, developed major complications, due in part to either stenosis at the site of anastomosis or a tendency to retraction out of the bowel with resultant fistula. Evidence of kidney damage, unilateral renal failure, or conditions necessitating decompression operations were all too frequent in the first group of 20 patients on whom this method of diverting the urinary stream was tried.

Because of the high incidence of complications we adopted the technique advocated by Leadbetter.[6] Here the ureter is made to pass through a wide tunnel beneath the seromuscular coat of the bowel. The full thickness of the ureter is then anastomosed to the mucosa of the bowel and the seromuscular coat closed tightly over it. A flap of peritoneum overlies the ureter and is sutured to the bowel to help seal the anastomosis and fix the bowel. The reduction in the number of major urinary complications has been gratifying.

During the past two years a left transverse colostomy has been performed above the ureterosigmoid anastomoses. The proximal end is turned in and restored to the abdominal cavity. The lower end of the sigmoid is brought out to the skin as before. The descending and sigmoid colon thus serves as a new bladder. This modification was designed primarily to enhance healing in the ureterosigmoid anastomosis by diverting the fecal stream during the critical postoperative period and, secondarily, to prevent future bouts of ascending pyelonephritis by providing an isolated loop for the anastomosis. No additional bowel anastomoses are necessary, the transverse colostomy does not run, and hyperchloremic acidosis does not occur. Time will indicate whether or not this additional step is necessary. The immediate reaction is favorable.

Hospital Mortality

The removal of all or most of the pelvic viscera is a formidable undertaking. There continues to be a high postoperative mortality. Any patient who failed to leave the hospital and return to her own home was classified as a postoperative death whether it occurred on the day of operation or two months later.

There were 24 hospital deaths in the total of 86 cases. The over-all mortality for the entire group is 28 per cent. There has been a decline in the operative mortality from 33 per cent in the first 43 cases to 23 per cent in the last 43 (Table II). Further experience may reduce this mortality figure still lower but in all probability it will remain relatively high. The patients have too much disease, radiation reaction, and kidney damage for us to expect that surgery of this magnitude can be done without mortality.

TABLE II. HOSPITAL MORTALITY IN 86 CASES OF PELVIC EXENTERATION FOR CARCINOMA OF THE CERVIX

NO. CASES	HOSPITAL DEATHS	PER CENT
Total 86	24	28
First 43 cases	14	33
Second 43 cases	10	23

In the past two and one-half years 27 total exenterations have been done for carcinoma of the cervix, utilizing a left transverse colostomy to delineate an isolated sigmoid loop. There have been only 5 hospital deaths in this group. It is interesting to note that in 29 ureterosigmoidostomies performed without transverse colostomy the hospital mortality was 38 per cent. In the last 27 total exenterations where transverse colostomy was performed the hospital deaths dropped to 19 per cent. The entire improvement cannot be attributed to the use of the colostomy alone. It is too early to be sure whether or not this trend will persist.

Survival

The average length of survival for treated patients in Stage IV is sixteen months. For the most part the patients in this present series represent treatment failures in Stage IV. The two series are therefore not comparable.

This is a new procedure. Arbitrarily, we have elected to evaluate pelvic exenteration for cancer of the cervix in terms of two-year survival, feeling that patients must live that length of time to justify the operation.

Sixty-three patients were operated upon two or more years ago and allow for some analysis of the factors influencing survival. There were 20 hospital deaths in this group. Of the 43 patients who left the hospital, 16 are alive two years or more after the operation (Table III). It is interesting to note that but one patient died after the two-year period who had not shown evidence of recurrence before two years. This patient succumbed six years after operation without local recurrence but with bone metastases. Two patients who died after two years showed no evidence of disease but extensive renal damage. We hope with improving techniques in ureteral intestinal anastomosis that such deaths will be avoided. The two-year survival period may be of importance in prognosis.

TABLE III. SURVIVAL FOLLOWING PELVIC EXENTERATION FOR CARCINOMA OF THE CERVIX (63 PATIENTS OPERATED UPON 2 YEARS AGO OR MORE)

Hospital deaths	20
Lived less than 2 years	20
Lived more than 2 years, dead	7
Living, 2 to 6½ years	16

Table IV presents the status of the 16 patients who are living from two to six and one-half years since operation. Nearly all have returned to full activity as housewife, mother, or wage earner. It is most gratifying to note that they have been able to return to a reasonably normal social existence. It is interesting to observe the mental adjustment to the altered physiological state. But two of the entire group showed any psychiatric unrest. The reactions were minimal. As the patient acquires increasing hope of survival she appears to take great pride in her ability to overcome her vicissitudes.

TABLE IV. STATUS OF 16 PATIENTS LIVING TWO OR MORE YEARS AFTER PELVIC EXENTERATION

CASE NO.	AGE	DISEASE	DATE	TYPE OF OPERATION	POSTOPERATIVE COURSE AND STATUS
14	61	Radiation ulcer	9/18/48	Total	Left nephrectomy, 1949. Now full activity
18	51	Stage IV	11/19/48	Total	Nonfunctioning left kidney, full activity
19	34	Radiation failure	2/16/49	Total	Skin ureterostomies. Full activity
22	42	Radiation failure	4/21/49	Total	Full activity
26	53	Bladder involvement	2/18/50	Partial	Pyelonephritis early, now well, full activity
27	59	Radiation failure	4/17/50	Total	Early pyelonephritis, now full activity
29	60	Stage IV	6/21/50	Total	Occasional pyelonephritis, full activity
34	36	Radiation failure	11/16/50	Total	Early pyelonephritis, full activity
35	58	Radiation ulcer	11/20/50	Total	Full activity
38	43	Bladder involvement	3/14/51	Partial	Full activity
41	48	Bladder involvement	6/ 4/51	Partial	Full activity
45	29	Radiation failure	7/24/51	Partial	Right nephrostomy, otherwise well
46	53	Radiation failure	7/18/51	Total	Perineal fistula, then skin ureter. Good
53	54	Post Wertheim hysterectomy	3/24/52	Partial	Early pyelonephritis, now well
58	64	Stage IV	12/17/52	Partial	Full activity
63	34	Stage IV	4/16/53	Total	Full activity

The wet colostomy formerly employed presented some difficulty in management at first but with time and experience the patient learns to control the elimination. The bowel habit is regulated by a combination of diet and irrigation so that one or two bowel movements a day are expected. Rarely is there a continual discharge of urine and feces as one might expect. Where a transverse colostomy has been performed the problem is, of course, nonexistent. The distal colon with ureters implanted acts as a urinary bladder. No instances of hyperchloremic acidosis have been noted nor do follow-up chemistry determinations suggest it in patients with either wet or transverse colostomy. It has been noted in the partial exenteration with an intact anal sphincter. General surgeons object to the transverse colostomy because of difficulty in regulating fecal drainage. It is the rare patient who has to wear a colostomy bag in the group of patients in this series in whom transverse colostomy has been done and a sigmoidal bladder created.

Nine of the 16 patients who survived for two years or more have had bouts of pyelonephritis and other urinary tract difficulties (Table IV). In most cases, however, this problem diminished with the passage of time and where periodic attacks have persisted these women are carrying on productive lives. The attacks are far less frequent when the transverse colostomy is done. In the group with wet colostomy who show any tendency to progressive destruction of kidney substance, transverse colostomies have been performed and the closed proximal end returned to the abdomen. The period of observation is short but follow-up pyelograms seem to suggest that bouts of pyelonephritis do not invariably lead to kidney destruction.

Twenty-seven patients succumbed after leaving the hospital, 20 within the first two years. The majority died within this period because of recurrence. Those who died within the first year had for the most part an extremely difficult and discouraging course. The convalescence was usually marked by recurring bouts of pyelonephritis or intestinal obstruction often requiring multiple hospital admissions. In general the result obtained was a severe drain both mentally and economically.

Most of the patients who survived between twelve and twenty-four months had a return to activity interspaced with hospital admissions. In this group there was real palliation.

Seven patients survived longer than two years to die later at 72, 42, 33, 32, 31, 29, and 26 months. Four had recurrence and 2 died of renal difficulties without evidence of recurrent or persistent malignant disease on postmortem examination. All had returned to active life until a few months before death. For the most part the recurrence was distant rather than local. Bone metastases were present in 4 cases. Only one patient died of late metastases (six years) who did not show evidence of recurrent disease before two years.

Over-all Survival

The over-all figures are shown in Table V. Of all patients operated upon over two years before, 37 per cent survived two years or more. Twenty-eight patients were operated upon over five years ago, and 7, or 25 per cent, lived over five years. One of these has since succumbed to recurrent disease six years after operation. The status of these six surviving patients has been presented in Table IV. Three more patients are living over four and one-half years since operation. Thus 10 of 37 patients operated upon over four and one-half years ago lived that long, while 9 are still living, active, and well.

If the patient can weather the surgical attack and leave the hospital, she has a 50 per cent chance of living two years and a 37 per cent chance of living five years.

The survival figures include death from all causes. Some of the deaths were postoperative, others were due to recurrent disease, including that group in whom operation was known to be ineffective in removing all the malignancy. It is hoped that better selection of cases, a continued decline in hospital mortality, and improved methods of dealing with the ureters to foretell future renal complications will all add up to a steady improvement in the over-all survival.

TABLE V. TWO- AND FIVE-YEAR SURVIVAL RATES FOLLOWING PELVIC EXENTERATION FOR CARCINOMA OF THE CERVIX

TOTAL		LIVED	PER CENT LIVED	LEFT HOSPITAL	PER CENT LIVED
2 to 5 years	63	23	37	43	53
		Living 16			
		Dead 7			
5+ years	28	7	25	19	37
		Living 6			
		Dead 1			

Extent of Operation and Survival

In the 64 cases of total pelvic exenteration there were 22 hospital deaths, or 34 per cent (Table VI). In 22 partial exenterations there were only 2 hospital deaths, or 9 per cent.

TABLE VI. EXTENT OF OPERATION AND HOSPITAL MORTALITY

	NO. CASES	DEATHS	PER CENT
Total	64	22	34
Partial	22	2	9

The advantage gained, however, by performing the less extensive and less hazardous procedure that preserves the rectum is apparently dissipated by the effect on survival. Table VII outlines the two- and five-year survival rates for the total and partial operations. There are more patients alive at two years following partial operation but no appreciable difference is noted in the five-year survival figures.

TABLE VII. EXTENT OF OPERATION AND SURVIVAL

	NO. CASES	LIVED 2 YEARS	PER CENT
Total	43	14	33
Partial	20	9	45
	NO. CASES	LIVED 5 YEARS	PER CENT
Total	22	5	23
Partial	4	1	25

It is conceivable that when sufficient cases have been followed over a five-year period we may find that the recurrence rate following partial exenteration for extensive carcinoma of the cervix will be so high, because of inherent pathways of spread of this disease, that the partial exenteration will have to be discarded or markedly limited in its application. Selection of the proper operation for the patient is a matter of surgical judgment.

There is one further element to consider. Among the 63 patients operated upon over two years ago, in 41 the indication was recurrence following radiation therapy. Many had several attempts at radiation after the initial failure. Eighteen were advanced or treated cases in Stages III and IV while 4 had

recurrence after a previous Wertheim type of radical hysterectomy (Table VIII). Contrary to expectations, the hospital mortality in the two groups is identical. The two-year survival group, however, is 11 per cent higher in the series of untreated cases. One should hasten to note, however, that there are only 2 partial exenterations among the 9 living cases of radiation failure; three of the 6 living patients in the previously untreated group had anterior exenterations.

TABLE VIII. RELATION OF SURVIVAL TO SELECTION IN 63 CASES OPERATED UPON OVER 2 YEARS AGO

	NO.	DEAD	LIVING
Radiation failure	41	13 (32%)	9 (22%)
Stages III and IV	18	6 (33%)	6 (33%)
Post Wertheim hysterectomy	4	1	1

Positive Nodes and Survival

We have been extremely interested in the presence of positive lymph nodes in relation to survival (Table IX). It is significant that of 63 patients operated upon two or more years ago only twenty-four, or 40 per cent, had positive pelvic lymph nodes. Thirty-nine, or 60 per cent, of these patients with extensive or recurrent carcinoma of the cervix still had negative lymph nodes at the time of operation. This is undoubtedly what makes this operation feasible.

TABLE IX. POSITIVE LYMPH NODES AND SURVIVAL IN 43 PATIENTS WHO LEFT THE HOSPITAL

	TOTAL	POSITIVE NODES	NEGATIVE NODES
Dead before 2 years	20	13	7
Dead after 2 years	7	3	4
Living more than 2 years	16	1	15
Total left the hospital	43	17	26

Of 17 patients with positive nodes who left the hospital, only 4 lived more than two years. Three died of recurrent disease before the third year was up. One still lives.

Of 26 who left the hospital with negative nodes, 19, or 73 per cent, lived two years or more, and 15, or 56 per cent, are still alive two or more years after operation.

The surviving patients, then, tended to have massive disease which spread in a fore-and-aft direction to involve rectum and bladder. The lateral spread appears to be more local than nodal. In many instances extensive risks are taken with the patient's life in order to eradicate masses of involved nodes densely adherent to the iliac vessels, particularly the internal iliac vein. This vein is so fragile and has so many branches that ramify through the cords of the sciatic nerve that massive hemorrhage may follow attempts to remove it in the interests of a clean pelvic wall dissection. One may then question the advisability of taking such risks if the chance of permanent cure is restricted by the presence of involved nodes. The answer to this question cannot be forthcoming from the limited material presented in this series.

Conclusion

Enough time has elapsed and enough operations have been performed to indicate that the pelvic exenteration has a definite place in the armamentarium

of treatment for cancer of the cervix. There is less evidence that it is of value for other forms of extensive pelvic malignancy. Patients can survive the operation and return to normal lives and be happy in their existence. There is a suggestion that the duration of this existence may be appreciable for a reasonable number of patients. There are many unanswerable problems in this experimental approach, but the initial results are encouraging.

We wish to express our gratitude to the Surgical and Nursing Staffs of the Massachusetts Memorial, Pondville Hospital, Department of Public Health of Massachusetts, Massachusetts General, and the Palmer Memorial Hospitals for the many hours spent in devoted care of these patients.

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Discussion

DR. HERBERT E. SCHMITZ, Chicago, Ill.—When evaluating the results of radical pelvic surgery, it is important to remember that those patients selected for such procedure are unquestionably doomed if nothing is done. This fact makes the high hospital mortality and the low five-year survival rate less appalling. We believe that all patients should be given an opportunity for cure. The risk involved should be presented to the patient and the choice should be hers.

Since 1947, we have performed 107 extensive operative procedures for recurrent or persistent carcinoma in patients previously irradiated to the limit of safety; 51 of these procedures were radical hysterectomy and pelvic lymph node dissection plus bladder resection, ureteral transplant into the bowel, pouch or cutaneous ureterostomies, and in some instances partial bowel resection and/or colostomy. Our efforts in these instances were to conserve bladder and bowel, if possible. There have been no operative or hospital deaths in this group, and 37 per cent of the group treated five or more years ago have survived. The salvage in this group could probably be enhanced by partial or total exenteration. However, they must be excluded in this present consideration.

Fifty-six patients were selected as possible candidates for pelvic exenteration (see Table I). It was possible to complete the contemplated surgery in 37. None of the cervix cases was treated with radical pelvic surgery as the primary procedure because the five-year survival rate for our irradiated Group IV cervix lesions remains at 10 per cent. We still employ irradiation as the initial therapy of choice since the primary surgical attack would raise this figure very little.

TABLE I

Total number of cases explored	56
Intended operation completed	37
Palliative procedure only	19

Employing the same criteria as the author, our hospital mortality rate for pelvic exenteration is 37.9 per cent (see Table II). The difference in hospital deaths between total and partial exenteration is listed in Table III. It can be seen that the posterior exenteration has been the most successful in our hands.

The number of cases is as yet too small to compare the five-year survival of total versus partial exenteration. The causes of death of the 14 patients who died in the hospital are listed in Table IV. Although the ultimate causes of death are multiple, it is our impression that the badly damaged kidney and the infected kidney are the greatest contributory factors to the high hospital mortality.

TABLE II. HOSPITAL MORTALITY IN 37 CASES OF PELVIC EXENTERATION FOR PELVIC MALIGNANCY

NUMBER OF CASES	HOSPITAL DEATHS	PERCENTAGE
37	14	37.9

TABLE III. EXTENT OF OPERATION AND HOSPITAL MORTALITY IN 37 CASES

EXENTERATION	NUMBER OF CASES	DEATHS	PERCENTAGE
Total	13	8	61.5
Anterior	14	5	35.7
Posterior	10	1	10.0

TABLE IV. CAUSES OF HOSPITAL MORTALITY IN 14 CASES

Pulmonary embolus	1
Peritonitis	1
Hepatitis	1
Hepatorenal syndrome	1
Uncontrollable postoperative oozing	1
Massive hemorrhage due to necrosis of iliac vessel	1
Pneumonia	1
Pyelonephritis	2
Anesthesia	2
Cardiac failure	1
Surgical shock	1
Uremia	1

Like Dr. Parsons, one of our greatest difficulties has been to find a satisfactory method of diverting the urinary stream. Dr. Parsons' technique of a left transverse colostomy above the ureterosigmoid anastomosis seems to be an excellent solution. It is similar to the Bricker pouch but eliminates the prolonged procedure required to isolate a loop of small intestine. When performed with partial exenteration, it has the advantage of continence as does the Gilchrist pouch but, again, is much simpler and consequently less time consuming. Our experience with the Gilchrist pouch has been somewhat disappointing since the procedure itself has a fairly high mortality rate in our hands. We have also had cases in which the ureter pulled out of the pouch with resulting fistula and ultimate loss of the kidney.

Cutaneous ureterostomies are definitely unsatisfactory. They are difficult for the patient to manage. In addition, the os tends to become stenosed and bouts of pyelitis are frequent.

The wet colostomy has also been disappointing. Kidney infection has been the greatest cause of difficulty. One patient died approximately a year after operation from a fulminating pyelonephritis that had been treated with small doses of sulfonamides by her family physician. On autopsy she was free of disease. A second patient died eight and one-half months following surgery because of uremia. Her damaged kidney with ureter implanted into the colon could not withstand the repeated bouts of bacterial invasion. Great care must be taken in the selection of the site for ureteral transplant when the kidneys are damaged. Such kidneys have very little chance of withstanding further insult.

We agree with Dr. Parsons that pelvic exenteration for malignancy other than of the cervix has been most discouraging. Only one patient of the group operated upon two years ago or more is living and well today; she has survived five years. The remaining patients died within two years following operation.

Our basic conclusions are in accord with those of Dr. Parsons. Pelvic exenteration does have a place in the treatment of pelvic cancer. The mere fact that a few of these hopelessly doomed patitents have returned to productive lives for a variable period of time makes further endeavor and improvement in this line imperative.

Of 37 patients upon whom we performed partial or total exenteration because of extensive pelvic malignancy persisting after irradiation, 11 have passed the five-year mark and, of these, 3 are alive and free of disease.

Dr. Joe V. Meigs, Boston, Mass.—Brunschwig has been criticized many, many times but I am sure, from the work that has been presented tonight by Dr. Parsons and Dr. Schmitz, that he has given us something that has helped people with usually hopeless disease. A certain number of these people are addicted to morphine. Some of the patients who live after their operations have a miserable existence, but to this group of people we could offer nothing previously. There are now quite a number who are going on and doing their jobs and doing them very well.

In 1941 in Excelsior Springs, I said to Dr. Dannreuther, "I am going to report a series of cases of cervical cancer operated upon by radical surgery, the so-called radical hysterectomy plus dissection of the pelvic lymph nodes." Dr. Dannreuther was not enthusiastic but told me to go ahead. When I first said that we should do more of this type of surgery I was afraid I might be hooted off the platform. It had been decided that there was only one way to treat carcinoma of the cervix and that was by radiation, and that is not true. I am convinced in my own mind that x-ray and radium have an important part in the treatment but that surgery has also. In Boston we now have a group attack on this disease. We have four hospitals combined in the attack. The Free Hospital for Women, the Peter Bent Brigham, the State Cancer Hospital at Pondville, and the Vincent Memorial Hospital (Massachusetts General Hospital)—all are together in an attack on this disease. I think maybe there are possibilities of increasing the salvage of these patients. When radiation treatment fails or when the sensitivity response (S.R.) or radiation response (R.R.) demonstrates that the patient will not respond, the patient is sent back for operation. To attack it without regard to sensitivity by surgery or radiation is wrong.

I am sure that there are not many people in this room who know how to do the Schauta or Schauta-Amreich operation. I have had the opportunity of being with Dr. Navratil and seeing how he does it. I do not believe you can do it without the proper instruments. In our patients who are radiation resistant and who are obese, have heart disease, or are poor risks, one cannot do a good radical abdominal operation. In such circumstances the Schauta operation should be used.

Dr. Ludwig Emge, San Francisco, Calif.—I wish I could join Dr. Meigs wholeheartedly in his enthusiastic evaluation of the exenteration procedure, so ably presented by Dr. Parsons, but I have my doubts about the logic as well as the efficacy of this ultraradical operation. I thought I noticed an undertone of doubt even in Dr. Parsons' remark about end results. If the operation is meant to prolong life, I venture to say that the end results hardly justify the procedure and, in fact, may not be in the best interest of the patient for, as I shall show you presently, man may live a long time with disseminated cancer. I do not mean to say that we should refrain from treatment if there is reasonable hope that life

actually could be prolonged or that great misery could be relieved permanently, but how rarely is this accomplished! Even if cancer is sure to kill, if not destroyed in toto, the exenteration operation, with its tremendous toll in terms of life, hardly looks like a promising venture. This thought is neither new nor original for you may read in the Aphorisms of Hippocrates that "it is better not to apply any treatment in cases of occult cancer (meaning disseminated cancer); for if treated, the patient often dies more quickly; but if not, he holds out for a long time and often with less anguish."

It may interest you that a rather high percentage of individuals suffering from cervix or corpus cancer may live an astonishingly long time without treatment. The California State Tumor Registry, under the able direction of Dr. James W. Ellis, has collected the following data which I am presenting with his permission:

CANCER PATIENTS REGISTERED BETWEEN 1942 AND 1946 AND FOLLOWED FOR FIVE YEARS AS OF 1951

TYPE OF CANCER	CORPUS	CERVIX	OVARY
Total Number	333	783	336
Per cent 5 year survival	40.8	34.4	20.2
Treated cases only	251	609	198
Per cent 5 year survival	47.8	40.0	34.3
Untreated cases	82	174	138
Per cent 5 year survival	19.5	13.8	none

It will be noted that the survival figures for all cases listed, as well as for those treated, are well in line with world-wide experience. However, the survival for five years or more of nearly 20 per cent of corpus cancer patients and nearly 15 per cent of cervix cancer patients who either refused treatment for reasons of their own or whose disease was considered too far advanced for treatment, certainly provides food for thought if one compares this experience with the survival of patients subjected to the radical exenteration operation as reported today by Dr. Parsons and others before him. Time does not permit delving deeper into the philosophic aspects of the ultraradical operation and its relation to its aim of prolonging life but the problem brings to mind Haldane's classical remark that "nothing but evil can come from forgetting that man must be looked at from many angles." This in no way reflects upon Dr. Parsons' excellent presentation but simply is meant to evoke further discussion.

DR. GEORGE V. SMITH, Brookline, Mass.—I am full of admiration at the accomplishments Dr. Parsons has just reported. Our experience with these procedures at the Free Hospital for Women has been much smaller, viz., 18 total pelvic exenterations and 28 partial. The group of partial exenterations is made up of such a variety of cancers and procedures that a report concerning it is hardly pertinent at present. Of the 18 cases of total exenteration performed during the past seven years, 13 had cancer of the cervix, 2 cancer of the ovary, 1 cancer of the endometrium, 1 cancer of the vagina, and 1 cancer of both the rectum and anus. There were 3 operative deaths; 14 left the hospital alive; 8 are alive today and 3 of the 6 operated upon more than 5 years ago are living without evidence of recurrence. The first total exenteration I did 7 years ago this month. The patient had had 3 previous operations for recurring pseudomucinous carcinoma of the ovary. When I saw her the bladder, vagina, and rectum were involved; the left kidney was functionless and the right kidney dilated. Despite occasional flare-ups of pyelonephritis, she is still doing quite well.

FURTHER RESULTS OBTAINED IN THE TREATMENT OF CANCER OF THE CERVIX WITH RADIOGOLD: A PROGRESS REPORT*

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THE present study of radioactive gold as an agent for the irradiation of the parametrium in carcinoma of the cervix began nearly five and one-half years ago. A year ago, we reported the results obtained in patients treated with gold and compared these results with those obtained in patients treated by x-ray and radium over the four years of 1950 through 1953. The report today covers the same patients, plus those treated during the year 1954.

There have been a few changes in the plan of treatment for the patients receiving gold. Initially, only good operative risks with Stage I lesions were treated with radiogold, the treatment consisting of the parametrial injection of gold followed by radical Wertheim hysterectomy and pelvic lymphadenectomy. Then, as experience was gained, poor operative risks were treated only with radiogold and radium. In the original group of 100 patients with Stage I and Stage II lesions, for example, there were only 30 patients in whom radical hysterectomy was not done. During the year 1954 there were 49 Stage I and II cases treated with radiogold. Of these 21 were subjected to operation and 28 were treated only with radiogold and radium. We hope, thereby, to gain added information regarding the value of completing treatment by operation. No Stage III cases have been operated upon as yet. Also, radium has been used for virtually all Stage I lesions and all Stage II and III lesions treated during the years 1951 through 1954. In general, patients subjected to operation have received less than 5,000 mg. hr. of radium while those not subjected to operation have received 6,000-8,000 mg. hr. of radium in two separate applications. The amount of gold injected has been usually 100-130 mc. divided equally between the two sides.

The results in Stage I cases are given in Table I. The results in the first year (1950) that we used radiogold seem the best. This is probably due to the selection of relatively early Stage I cases for treatment with gold. Since that time, however, virtually all Stage I cases have been treated with gold regardless of the size of the primary lesion. In this group there are two cases lost to follow-up, one treated in 1953 and one in 1954, and both are presumed to be alive without disease as judged by the last visit to the clinic. The survival rate in the clinic group treated with x-ray and radium is better than that reported a year ago because two patients reported as lost to follow-up have since been located and are now reported as alive and well. The over-all ½ to

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5½ year survival rate is 90.8 per cent in the radiogold group, 80.0 per cent in the private group treated with x-ray and radium, and 74.2 per cent in the small clinic group treated with x-ray and radium.

TABLE I. STAGE I

YEARS OF TREATMENT	X-RAY AND RADIUM						Au^{198} ± RADIUM WERTHEIM		
	CLINIC			PRIVATE			CLINIC AND PRIVATE		
	NO. TREATED	ALIVE WITHOUT DISEASE		NO. TREATED	ALIVE WITHOUT DISEASE		NO. TREATED	ALIVE WITHOUT DISEASE	
		NO.	PER CENT		NO.	PER CENT		NO.	PER CENT
1950	17	13	76.5	8	6	75.0	13	13	100.0
1951	8	6	75.0	21	16	76.1	15	12	80.0
1952	4	2	50.0	12	9	75.0	16	15	93.7
1953	3	3	100.0	15	12	80.0	19	17	89.5
1954	3	2	66.6	14	13	92.8	24	22	91.7
Total	35	26	74.2	70	56	80.0	87	79	90.8
Lost to follow-up		1						2	
Alive with disease									

The results in Stage II cases are given in Table II. It is apparent here, just as in the Stage I lesions, that better results were obtained in the first cases treated. This, too, is probably due to very careful selection of the cases during the first two years of the study. During the past two years, including 1955, about three-fourths of our Stage II cases have been treated with radiogold. It seems probable, however, that in the entire five-year period there has not been too much selection of the more favorable cases for treatment with gold since the survival rate in the remainder of the clinic group treated with x-ray and radium is virtually the same as the survival rate in the private group when all patients were treated with x-ray and radium. The survival rate in the clinic group treated with x-ray and radium was 55.1 per cent, and in the private group where there was no segregation of the cases at all, the rate was 58.7 per cent. The figures seem significantly lower than the survival rate of 88.7 per cent in the cases treated with radiogold.

TABLE II. STAGE II

YEARS OF TREATMENT	X-RAY AND RADIUM						Au^{198} ± RADIUM WERTHEIM		
	CLINIC			PRIVATE			CLINIC AND PRIVATE		
	NO. TREATED	ALIVE WITHOUT DISEASE		NO. TREATED	ALIVE WITHOUT DISEASE		NO. TREATED	ALIVE WITHOUT DISEASE	
		NO.	PER CENT		NO.	PER CENT		NO.	PER CENT
1950	12	7	58.3	11	6	54.5	4	4	100.0
1951	19	8	42.1	17	11	64.7	2	2	100.0
1952	15	6	40.0	14	6	42.8	11	10	90.9
1953	8	6	75.0	23	12	52.2	20	17	85.0
1954	15	11	73.3	15	12	80.0	25	22	88.0
Total	69	38	55.1	80	47	58.7	62	55	88.7
Lost to follow-up		1						1	
Alive with disease		2						1	

The results in Stage III cases are given in Table III. This table shows that only in the past two years has any serious attempt been made to treat many Stage III cases with radiogold. The results with gold seem good. How-

TABLE III. STAGE III

YEARS OF TREATMENT	X-RAY AND RADIUM						Au^{198} ± RADIUM WERTHEIM		
	CLINIC			PRIVATE			CLINIC AND PRIVATE		
		ALIVE WITHOUT DISEASE			ALIVE WITHOUT DISEASE			ALIVE WITHOUT DISEASE	
	NO. TREATED	NO.	PER CENT	NO. TREATED	NO.	PER CENT	NO. TREATED	NO.	PER CENT
1950	7	3	42.8	7	0	0.0	0	0	
1951	10	2	20.0	2	1	50.0	2	1	50.0
1952	12	3	25.0	6	1	16.7	2	1	50.0
1953	11	2	18.2	4	2	50.0	12	6	50.0
1954	8	3	37.5	6	5	83.3	11	8	72.7
Total	48	13	27.1	25	9	36.0	27	16	59.2
Lost to follow-up								1	
Alive with disease		4						1	

ever, a more careful perusal of the table immediately brings out the fact that 23 of the 27 cases treated with gold were treated in the past two years.

The over-all salvage in all three classes of patients, clinic treated with x-ray and radium, private treated with x-ray and radium (all private patients of Dr. A. N. Arneson), and the group (both clinic and private) treated with radiogold are given in Table IV. The upper half of the table gives the results for the five-year period (1950-1954) and the lower half the results for the four-year period (1950-1953). The most important part of the table is to be found in the second half pertaining to Stages I and II. It is evident that 90 of 100 patients (Stages I and II combined) are alive and presumably free of disease from 1½ to 5½ years after treatment. This seems especially significant because we have as yet lost no patient in the radiogold group longer than 1½ years after treatment. This second half of the table, of course, contains the data pertaining to the same patients reported last year. Comparison of this year's with last year's report shows that there is one Stage I case listed last year which is missing this year. This patient is, we hope, only temporarily lost to follow-up. Other than this one, all Stage I and II patients reported as alive without disease a year ago are still alive without disease.

The results obtained in the entire group treated with radiogold are given in Table V. The data are so arranged that the three different methods of

TABLE IV.

CLINICAL STAGE	X-RAY AND RADIUM						Au^{198} ± RADIUM WERTHEIM		
	CLINIC			PRIVATE			CLINIC AND PRIVATE		
		ALIVE WITHOUT DISEASE			ALIVE WITHOUT DISEASE			ALIVE WITHOUT DISEASE	
	NO. TREATED	NO.	PER CENT	NO. TREATED	NO.	PER CENT	NO. TREATED	NO.	PER CENT
½ to 5½ Year Survivals.—									
I	35	26	74.2	70	56	80.0	87	79	90.8
II	69	38	55.1	80	47	58.7	62	55	88.7
III	48	13	27.1	25	9	36.0	27	16	59.2
Total	152	77	50.6	175	112	64.0	176	150	85.2
1½ to 5½ Year Survivals.—									
I	32	24	75.0	56	43	76.7	63	57	90.4
II	54	27	50.0	65	35	53.8	37	33	89.2
III	40	10	25.0	19	4	21.1	16	8	50.0
Total	126	61	48.4	140	82	58.5	116	98	84.4

treating these patients can be compared. First, it appears that the results are as good in those patients treated with radiogold and radium but without surgery, as in those in whom treatment was completed by radical Wertheim hysterectomy and pelvic lymphadenectomy. This, however, may not be a valid conclusion since 28 of the 58 cases not subjected to operation were treated in 1954 and insufficient time has passed to judge the effectiveness of treatment. Second, one cannot assume that radium is unnecessary since 30 of the 31 cases treated with radiogold and surgery, but without radium, were Stage I cases. Third, 7 of the 11 patients who have succumbed are known to have had widespread carcinomatosis at the time of death. It is probable also that the two who died of unknown causes had carcinomatosis. We suppose that these patients were lost because the disease was already disseminated at the time of treatment. Unfortunately, autopsies have not been obtained in all cases. In one patient, however, with positive nodes at the time of exploration (Wertheim was not done), who died within six months of metastases to the lungs and brain, no residual tumor was present in the remaining lymph nodes or the cervix.

TABLE V. SUMMARY OF STAGE I AND II CASES, ½ TO 5½ YEARS

	RADIOGOLD AND SURGERY	RADIOGOLD AND RADIUM AND SURGERY	RADIOGOLD AND RADIUM	TOTAL
Number treated	31	60	58	149
Number alive without disease	28	55	51	134
Per cent alive without disease	90.3	91.6	87.9	89.9
Fate of those lost				
Died, carcinomatosis	2	3	2	7
Died, late complications with tumor	0	0	0	0
Died, late complications without tumor	0	0	2	2
Died, cause unknown	1	1	0	2
Alive with disease	0	0	1	1
Lost to follow-up	0	1	2	3
Total	3	5	7	15

All deaths occurred in less than 1½ years.

The incidence of positive nodes is given in Table VI. In the 91 patients subjected to operation, 17 have had positive nodes and of these only 3 have died, and these 3 died relatively soon of carcinomatosis.

TABLE VI. RESULTS IN PATIENTS WITH POSITIVE LYMPH NODES TREATED BY WERTHEIM AND LYMPHADENECTOMY FOLLOWING INJECTION OF Au^{198}

STAGE	NO. TREATED	INCIDENCE OF POSITIVE NODES		ALIVE WITHOUT DISEASE	
		NO.	PER CENT	NO.	PER CENT
I	66	8	12.1	6*	75.0
II	25	9	36.0	8*	88.8

*All three patients died with generalized carcinomatosis.

The genitourinary complications are given in Table VII. Three patients have had serious ureteral strictures, 3 have had ureteral fistulas, and one has had a vesicovaginal fistula. These 7 cases occurred in the 60 treated with radiogold, radium, and operation. Since no serious injury to the ureters or bladder appeared in 31 cases treated with gold and operation, but without radium, and since no serious injury appeared in 58 cases treated with gold

and radium but without operation, it seems fairly obvious that the addition of both radium and surgery to the use of gold materially increases the likelihood of serious injury to the ureters.

TABLE VII. GENITOURINARY COMPLICATIONS

STAGE	METHOD OF TREATMENT	NO. TREATED	ALIVE WITHOUT DISEASE		SERIOUS GENITOURINARY COMPLICATIONS
			NO.	PER CENT	
I	Au^{198} + operation	30	27	90.0	1. Ureteral stricture—resection 2. Ureteral stricture—ileobladder 3. Ureteral stricture—nephrectomy 4. Ureteral fistula—ileobladder
	Au^{198} + radium and operation	36	33	91.6	
	Au^{198} + radium alone	21	19	90.4	
II	Au^{198} + operation	1	1	100.0	1. Ureteral fistula—ileobladder 2. Ureteral fistula—ureterosigmoid anastomosis 3. Vesicovaginal fistula—ileobladder
	Au^{198} + radium and operation	24	22	91.6	
	Au^{198} + radium alone	37	32	86.4	

Finally, we have arranged the data in Table VIII in such a way that the question of selection of cases can be appraised. On the left side of the table are found all Stage I, II, and III cases which have been treated in our tumor clinic.

TABLE VIII. COMPARISON OF CASES AND RESULTS, 1½ TO 5½ YEARS

STAGE	COMBINED CLINIC CASES TREATED BY BOTH METHODS*			PRIVATE CASES TREATED BY X-RAY AND RADIUM		
	NO. TREATED	INCIDENCE OF STAGE PER CENT	ALIVE WITHOUT DISEASE PER CENT	NO. TREATED	INCIDENCE OF STAGE PER CENT	ALIVE WITHOUT DISEASE PER CENT
I	95	39.3	85.3	56	40.0	76.7
II	91	37.6	65.9	65	46.4	53.8
III	56	23.1	32.1	19	13.6	21.1
Total	242	100.0	65.7	140	100.0	58.5

*Includes all clinic cases treated with x-ray and radium plus clinic and private cases treated with radiogold ± radium and surgery.

These 242 cases include all clinic cases treated with x-ray and radium, plus all cases treated with radiogold. On the right side are all the private cases of Dr. Arneson treated only with x-ray and radium. No Stage IV cases are listed as in the clinic, and in Dr. Arneson's private cases Stage IV cases are those that already had distant metastases or rectovaginal or vesicovaginal fistulas when first seen. This table shows, first, that the clinic group contains a higher percentage of Stage III's than the private group but shows little difference in the ratio of Stage I to Stage II. Second, it is apparent that the over-all salvage in the clinic group for all stages is better than the salvage in the private group. This increased salvage is due entirely to the better results in the cases treated with gold, since the results in the clinic group treated with x-ray and radium are about the same as in Dr. Arneson's private cases.

Again, as we said last year, we have no conclusion to make beyond the obvious one that we seemingly have had better results in patients treated with radiogold than we have had in patients treated during the same period of time with x-ray and radium or in patients treated prior to this study with x-ray and radium.

OXYGEN UTILIZATION BY THE HUMAN FETUS IN UTERO*†

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THE very nature of intrauterine existence implies an evolutionary series of physiologic mechanisms which provide the fetus with both temporary and permanent functions and, in the final analysis, prepare it for extrauterine life. Presumably the special qualities which direct the activity of the fetal physiologic systems are integrated with the functional capacity of the placenta. Thus, according to a recent in vitro study, the human placenta begins to relinquish its role of storing glycogen and secreting glucose sometime near the fifteenth week of pregnancy when the fetal liver acquires the biochemical mechanisms essential to the performance of carbohydrate metabolism.[1]

An understanding of the fetal biochemical patterns is essential to an appraisal of the factors which cause a departure from normal embryonal development and to evaluate the ability of the fetus to adapt to physiologic alterations in environment. The purpose of this report is to present one aspect of intrauterine physiology, namely, an approximation of the oxygen utilization and the total oxygen consumption of the term fetus in utero.

Studies of the oxygen content of blood in the umbilical artery and vein demonstrate the levels of oxygen tension at which the fetal blood secures and releases the gas, but they afford no information of the fetal oxygen consumption. Measurements of the oxygen and carbon dioxide content of the umbilical vein and artery blood at birth have been reported by several investigators.[2-4] Although the values have varied widely, these studies establish the fact that in normal term pregnancy the fetal blood in the umbilical vein has an oxygen content of approximately 50 per cent of capacity. Despite this low oxygen tension, the fact that the arteriovenous oxygen difference of umbilical blood is 4 to 5 volumes per cent demonstrates that the fetal blood has the faculty both of absorbing oxygen and of releasing it readily to the tissues. Indeed, where hypoxia is extreme, it has been demonstrated that the fetal blood can divest itself completely of oxygen in an attempt to prevent damage from anoxia to the tissues.[5]

To determine the fetal consumption of oxygen by sampling the oxygen content of the umbilical vessels, the minute volume of the fetal circulation

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**This work was done during the tenure of an Investigatorship of the United States Public Health Service.

***This work was done during the tenure of an Established Investigatorship of the American Heart Association.

must be known. An attempt has been made to measure the velocity of fetal circulation at cesarean section by the introduction of Congo red dye into the pulsating umbilical vein. It was suggested that the oxygen content of the umbilical blood was inversely related to the rate of fetal blood flow, but no data were presented or reference made to the circulating minute volume.[6] In other studies, crude estimates have been made of the oxygen consumption of the human fetus by assuming that the minute volume of the fetal circulation is comparable to that found in the sheep by Barcroft and Huggett. More recently, from a study concerned with measuring the rate of uterine blood flow, the total oxygen consumption of the human uterus and its contents was calculated to be 14 to 24 c.c. per kilogram per minute, or some 3 to 5 times the rate of oxygen consumption of the mother.[7]

Materials and Results

In the course of a study of uterine blood flow, the results of which have been reported previously,[8, 9] data were obtained which offered an opportunity to calculate the total amount of oxygen consumed by the term fetus prior to its removal from the uterus at repeat cesarean section performed under spinal anesthesia. Knowing the volume of uterine blood flow, the total uterine oxygen consumption can now be determined, it being the product of the uterine blood flow and the oxygen difference between the uterine artery and vein.

The volume of uterine blood flow is calculated by measuring the nitrous oxide difference between maternal brachial artery blood (all arteries have the same oxygen content) and uterine venous blood over a thirty-minute period of administration of 15 per cent nitrous oxide to the mother. The uterine venous blood is sampled through a polyethylene catheter inserted under direct vision into a parametrial vein and threaded into the uterine vein. Venous samples, drawn anaerobically, are analyzed for nitrous oxide, oxygen, and carbon dioxide content. The nitrous oxide content of maternal arterial and uterine venous blood is plotted against time and a set of curves is obtained. Determination of the area between these curves gives the total arteriovenous nitrous oxide difference of the uterus and its contents. Calculation of the uterine blood flow also requires that the nitrous oxide content of the uterus at the end of the period of administration of nitrous oxide be known. This has been estimated by adding the nitrous oxide contents of the fetus, the placenta, myometrium, and amniotic fluid. These components are estimated by knowledge of the nitrous oxide concentrations in umbilical arterial blood, maternal arterial blood, amniotic fluid, and the weights or volumes of each. The assumptions involved are based on the averages of large numbers of observations. Contrary to the findings in another study,[7] nitrous oxide never reached equilibrium in these experiments even thirty minutes after the beginning of the administration.

Upon completion of this period of nitrous oxide inhalation, the fetus is delivered by hysterotomy and every effort made to obtain a segment of umbilical cord before the initial inspiratory gasp of the infant occurs. Anaerobically drawn blood samples are obtained from the umbilical vein and artery and also analyzed for nitrous oxide, oxygen, and carbon dioxide.

The procedure has been attempted in 27 women, one of whom had a twin pregnancy, and 14 of these cases comprised the material for the report on measurement of uterine blood flow.[8, 9] There have been no puerperal complications in the postoperative period in any of the women studied, and the neonatal course of each infant delivered has also been without event. Thirteen of the reported cases are included in this study for the observations are suffi-

ciently complete to permit the calculation of the supplementary fetal oxygen data. In 4 of the cases, the contents of the umbilical artery could not be successfully sampled. The anaerobic sampling of the umbilical vessels for their oxygen content is fraught with many potential difficulties; hence the previously reported values of oxygen content in the umbilical vein and artery show a considerable range.[4] In this report, with respect to oxygen, it was thought best to present the values actually obtained rather than only average interpretations.

The availability of these data allows calculation of the coefficient of oxygen utilization by the uterus and its contents, and the fetus. The coefficient of oxygen utilization, by definition, expresses the proportion of total oxygen content of the blood given up to any tissue or organ. If the oxygen contents of the uterine artery and vein are known, this allows for the calculation of the oxygen coefficient of the uterus, i.e., $\frac{O_2 \text{ difference uterine artery} - \text{uterine vein}}{O_2 \text{ content uterine artery}}$, and of the fetus, i.e., $\frac{O_2 \text{ difference umbilical vein} - \text{umbilical artery}}{O_2 \text{ content umbilical vein}}$.

Results

Table I presents the oxygen contents of uterine artery and vein, as well as their related rates of uterine blood flow. The oxygen consumption of the uterus and its entire contents, as well as a breakdown in terms of oxygen consumed per kilogram of tissue involved, is also listed.

TABLE I. UTERINE ARTERIAL AND VENOUS OXYGEN CONTENT AND RELATED FIGURES

EXPERIMENT NUMBER	FETAL WEIGHT (KG.)	OXYGEN CONTENT UTERINE ARTERY (C.C./100 3.3)	OXYGEN CONTENT UTERINE VEIN (C.C./100 C.C.)	A-V OXYGEN DIFFERENCE (C.C./100 C.C.)	UTERINE BLOOD FLOW (C.C./ MINUTE)	UTERINE OXYGEN CONSUMPTION (C.C./ MINUTE)	UTERINE OXYGEN CONSUMPTION / FETAL WEIGHT* (C.C./ MINUTE/ KG.)
7	3.5	17.5	14.5	3.0	590	17.7	3.5
8	3.1	15.4	12.0	3.4	535	18.2	4.0
10	3.0	13.7	8.7	5.0	330	16.4	3.6
11	3.2	15.1	11.3	3.8	560	21.3	4.4
12	3.1	13.9	10.5	3.4	480	16.4	3.6
14	3.6	15.2	9.1	6.1	510	31.0	6.1
16	3.7	14.0	9.3	4.7	315	14.8	2.9
18	3.7	15.2	12.5	2.7	840	22.7	4.4
19	2.9	14.1	9.0	5.1	255	13.0	3.0
21	3.2	16.7	10.4	6.3	770	48.5	10.3
24	3.5	16.1	9.8	6.3	700	44.0	8.8
25	2.9	15.5	9.0	6.5	335	21.8	4.9
20 (twins†)	3.6 3.3	13.3	9.1	4.2	1156	48.3	5.3
Average	3.3	15.2	10.5	4.7	518	23.8	5.0

*Fetal weight plus uterine weight (1 kilogram) plus placental weight (0.5 kilogram).
†Twins are not included in the averages.

The uterine blood flow is in the order of magnitude of 500 c.c. per minute. The average oxygen contents of uterine artery and vein are 15.2 c.c./100 c.c. and 10.5 c.c./100 c.c., respectively. The total oxygen consumption of the uterus and contents averages between 20 and 25 c.c. per minute. There is considerable variation in the extremes of the values reported. The experiments were considered valid and the results checked in duplicate, however. These are reported without selection since the impression exists that many

transient or sampling factors could affect the oxygen consumption. However, these factors remain to be evaluated in studies which are continuing. It is noteworthy that the twin pregnancy had a uterine blood flow and an oxygen consumption of approximately twice that of the single pregnancies.

Table II lists the data related to the oxygen content of the fetal blood. For comparative purposes the arteriovenous oxygen difference between the uterine artery and vein is compared with the difference existing between umbilical vein and artery. The average oxygen content of 8.0 volumes per cent in umbilical vein compares favorably with the lower of such values previously reported. There is an impression that lower values of oxygen content probably are more accurately representative of the conditions in utero since factors of manipulation of the cord, uterus, or sampling contribute to increasing the values obtained. The average oxygen content in the umbilical artery was 3.6 volumes per cent. Included in it is Experiment No. 24, in which the oxygen content of the umbilical artery was measured at 7.4 volumes per cent, providing an arteriovenous difference of only 0.1 volumes per cent. It is possible that the umbilical vein was twice sampled in error in this experiment. This could not be substantiated, however, nor was any error reported at the time of collection. Hence it is included.

TABLE II.—UMBILICAL ARTERIAL AND VENOUS OXYGEN CONTENT

EXPERIMENT NUMBER	FETAL WEIGHT (KG.)	UMBILICAL VEIN (C.C./100 C.C.)	UMBILICAL ARTERY (C.C./100 C.C.)	MATERNAL A-V OXYGEN DIFFERENCE (C.C./100 C.C.)	FETAL A-V OXYGEN DIFFERENCE (C.C./100 C.C.)
7	3.5	11.5	—	3.0	—
8	3.1	10.4*	2.9	3.4	7.5
10	3.0	8.2*	3.1	5.0	5.1
11	3.2	10.2*	4.9	3.8	5.3
12	3.1	7.5*	2.3	3.4	5.2
14	3.6	—	—	6.1	—
16	3.7	11.1	—	4.7	—
18	3.7	5.6	—	2.7	—
19	2.9	6.4	—	5.1	—
21	3.2	5.6*	1.7	6.3	3.9
24	3.5	7.5*	7.4	6.3	0.1
25	2.9	7.3*	2.7	6.5	4.6
20 (twins†)	3.6	10.3	—	—	—
	3.3	7.7*	3.2	4.2	4.5
Average	3.3	8.0*	3.5	4.7	4.5

*Cases included in computing the average oxygen content of the umbilical vein.
†Twins are not included in the averages.

TABLE III. COEFFICIENT OF OXYGEN UTILIZATION

EXPERIMENT NUMBER	FETAL WEIGHT (KG.)	O_2 DIFFERENCE UT. ART.–UT. VEIN / O_2 CONTENT UTERINE ARTERY	O_2 DIFFERENCE UMB. VEIN–UMB. ART. / O_2 CONTENT UMBILICAL VEIN
7	3.5	.171	—
8	3.1	.221	.721
10	3.0	.364	.621
11	3.2	.251	.519
12	3.1	.244	.693
14	3.6	.401	—
16	3.7	.335	—
18	3.7	.177	—
19	2.9	.361	—
21	3.2	.377	.696
24	3.5	.391	.013
25	2.9	.412	.630
20	3.9	.315	.584
	3.3		
Average		.309	.560

Table III represents a comparative listing of the calculated coefficient of oxygen utilization for the uterus and fetus. There is a tendency toward a higher coefficient going in the direction from uterus to fetus. The coefficient for each structure in the various experiments is fairly constant and the differences appear to be related to the rate of uterine blood flow or to the basic content of oxygen in the artery and vein of the uterus or of the umbilical vessels of the fetus. Thus, again in Experiment No. 24, the fetal coefficient of oxygen utilization is almost nonexistent and is related to the high oxygen content of the umbilical artery.

Comment

Data have been presented from 13 human term pregnancies studied at cesarean section under spinal anesthesia. The volume of uterine blood flow has been measured by a modification of the Kety adaptation of the Fick principle, involving the inhalation of 15 per cent nitrous oxide. The average uterine blood flow has been found to be about 500 c.c. per minute, while in the case of a twin pregnancy the amount of blood flow was doubled. Since the average oxygen difference between uterine artery and uterine vein is 4.7 volumes per cent, and the average combined weight of the fetus, uterus, and placenta is 4.8 kilograms, it is to be noted that the average oxygen consumption of the pregnant uterus is about 23.5 c.c. per minute and the average oxygen consumption per kilogram of fetal tissue is approximately 5.0 c.c. per minute.

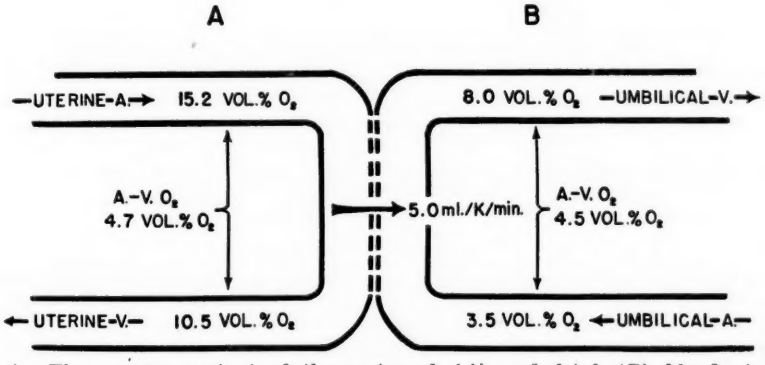

Fig. 1.—The oxygen content of the maternal (*A*) and fetal (*B*) blood at term.

The distribution of uterine blood to the placenta as compared to extraplacental channels is not known and cannot be obtained by the method currently employed. The in vitro oxygen consumption of wet placental tissue from term pregnancy has been shown to be about 4.5 c.c. per kilogram per minute,[10] and the consumption of the myometrium is probably of about the same order of magnitude. In making the calculation, it has been assumed that the myometrium, the placenta, and the fetus utilize oxygen in proportion to their relative weights. Thus it is evident that a minimum of 5 c.c. of oxygen crosses the placenta each minute for each kilogram of fetal weight, and that approximately 25 per cent of the total uterine oxygen consumption is probably consumed by the myometrium and placenta. The oxygen arteriovenous differences of the uterine artery and vein and the umbilical artery and vein in this series are almost identical in value (Fig. 1). This appears to indicate in accordance with the Fick principle that the volume of fetal blood flow to the placenta

closely approximates that which the mother supplies to this organ. These data are in essential agreement with results previously obtained by other methods in animals, and indicate a rapid rate of flow at term for the fetal circulation.

It is thought that a significant percentage of fetal energy is derived through anaerobic metabolism.[4, 11] Evidence for this belief is based on the fact that the pyruvic and lactic acid content of the cord blood is elevated above the levels in the maternal blood.[12] The fetus, moreover, has a greater resistance to anoxia, and the resistance varies inversely with its maturity. Further, this increased resistance to oxygen deficit can be abolished experimentally in the newborn animal by the inhibition of glycolysis or the anaerobic component of carbohydrate metabolism.[13] Consequently, other workers have assumed that the fetus uses less oxygen than the mother per unit weight, and accordingly, oxygen consumption of the fetus has been estimated to be one-fourth or one-fifth that of the newborn.[6]

There is evidence to support the concept that in early fetal life anaerobic metabolism, especially during the crucial period of organogenesis, may provide an important source of energy for fetal growth and development. Recently, in vitro studies have demonstrated some of the properties and reactions of fetal tissue in an anaerobic and aerobic environment. Accordingly, the human fetus contains a lactic dehydrogenase enzyme system by at least the seventh week of intrauterine life.[14] Furthermore, in most of the tissues studied, lactate utilization was constant throughout pregnancy and did not vary in fetuses from 7 to 40 weeks' gestational age.[14] Equally important, fetal tissue produced lactate at the same rate and in equal amounts in aerobic as under anaerobic conditions.[14, 15] These data imply that, from the very beginning of its embryonal development, the fetus can carry on an anaerobic type of metabolism which apparently continues to operate at a constant level of activity throughout the course of pregnancy. The placenta likewise participates in glycolytic activity, a property which it tends to lose late in pregnancy.[10]

The coefficient of oxygen utilization for the fetus is significantly higher than that of the uterus. In other words, the fetus uses a higher proportion of the oxygen available in the umbilical blood than the uterus and its contents extract from the uterine blood stream. The coefficient of oxygen utilization varies considerably for different tissues and for the same tissues at different times in accordance with increased activity and alterations in the rate of blood flow. While the nature of changes in fetal blood flow is not known, the fact that the fetal oxygen coefficient is increased over that of the uterus is indicative that the fetus has abstracted a greater quantity of oxygen from a given volume of blood. Thus, based on fetal oxygen consumption and the index of oxygen utilization, the evidence is clear-cut that the fetus in utero has available to it and uses a considerable amount of oxygen.

The energy needs of the fetus will depend in large measure upon its rate of growth. In the latter weeks of pregnancy this is markedly accelerated and an increase in total oxygen consumption may be anticipated. Much of the increase in weight, however, is the result of deposition of fat which requires some amount of glycolysis for the synthesis of fatty acids.[16] To what extent aerobic metabolism is concurrently increased during this period requires investigation. Until the source and amount of energy expenditure are known for the fetuses of different ages, what constitutes a state of fetal oxygen deficit must remain speculative. From these studies, however, we conclude that the term fetus has an oxygen consumption comparable to that of its mother.

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Discussion

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—The experiments of Dr. Reid and his co-workers constitute the first major attack on the subject of uterine blood flow and oxygen utilization. As such they are important foundation stones in an understanding of conditions which affect fetal welfare in utero.

There is little justification for my undertaking to discuss this new and unparalleled work other than the similarity of method which was observed in Dr. McCall's work on cerebral *vascular* circulation as conducted in our Department at The Jefferson Hospital, and our present interest in oxygen saturation studies of the fetus under various conditions of labor and various forms of delivery.

In this field experimentation and interpretation are both difficult. Technical procedure is exacting, results are widely variable, and interpretation of the many subtle factors which may influence levels in pregnancy or labor is difficult.

For instance, in a study of this kind, it is questionable as to what constitutes the fundamentally normal. Is it the average of results, the high group, or the low group of observations? In Dr. Reid's results the arteriovenous oxygen differences in the case of uterine blood flow vary from each other in extreme cases by as much as 150 per cent, and in the case of the cord vessels by as much as 100 per cent. Uterine oxygen consumption

per unit of fetal weight is in some instances 3 to 4 times greater than in others, yet these were all repeat cesarean sections near term and in all these varied instances the baby appeared to be healthy, and survived.

Between investigators also there is a substantial difference of results in respect to such a simple procedure as sampling of the cord vein and artery at the moment of delivery. In general, determinations of venous content of oxygen and vein-artery differences have been higher than Dr. Reid has found. Technical procedure in collection and analysis may explain some of this difference of results but method of delivery and type of anesthesia have also an important bearing.

For instance, the question may be raised whether determinations made under spinal anesthesia with the uterus exposed to air during twenty to thirty minutes of observation represent suitably the situation that exists in the full-term undisturbed pregnant uterus.

Our own results, as recorded in cesarean section, indicate a lag of 10 per cent in oxygen saturation of fetal blood all along the line. For this and other reasons we doubt that spinal anesthesia is the preferred agent in cesarean section. Actually the best results have been noted in spontaneous delivery in the lateral position.

Several observers have also commented that exposure of the uterus to the air, particularly in spinal and local anesthesia, has led to tetanic contraction which probably impairs uteroplacental exchange of gases. Possibly both of these factors combine to make Dr. Reid's results quite variable and unusually low.

We have aspirated blood from the cord vein at the moment of birth and 15 minutes later in an effort to determine what effect the early efforts of fetal respiration and the contraction of the uterus after delivery of the baby have upon the oxygen content of the cord vein. These results indicate that usually the oxygen content of the cord vein is lower after 15 minutes than it was at the moment of delivery.

Our figures are higher than the average and are not without the possibility of technical error in collection though checked in determination frequently between the Van Slyke and the Kopp-Netelson apparatuses. The spontaneous deliveries were performed, however, without analgesia or anesthesia. I suspect that the actual oxygen content of fetal blood in utero may be higher in late pregnancy than is suggested by determinations of clamped cord segments after labor in vaginal delivery or as noted in cesarean sections under spinal anesthesia.

All of this, however, has nothing to do with the importance of securing further knowledge of uterine and placental circulation; it is only to point out some of the obvious pitfalls of experimental method in a difficult field. It will of course require many observations under many conditions before one can relate the variability of results to the variability of the many influencing factors in human gestation. This, I believe, Dr. Reid and his fellow workers are undertaking to do. The observations that were made in twin pregnancy illustrate an intriguing example of this correlation.

DR. NICHOLSON J. EASTMAN, Baltimore, Maryland.—Does the fetus under normal conditions exist in a state of oxygen or, to phrase it differently, does the fetus under normal conditions resort to anaerobic metabolism? The evidence to support any such hypothesis has always impressed me as being very meager. Studies have appeared dealing with the lactic acid content of the umbilical vein and artery blood and these, in general, show little significant increase in the lactic acid content of the umbilical vein or artery blood over that of the mother. This fact plus the findings of Dr. Reid would lead us to believe that under normal circumstances, although the fetus may well exist near the border line of hypoxia, it nevertheless utilizes an amount of oxygen comparable to that utilized by the mother. What I have said applies to the fetus under normal conditions, but we are all aware that normal intrauterine conditions do not always obtain. Indeed, there is a variety of pathologic states which impose a grave state of hypoxia now and then on the fetus. This threat of hypoxia to the fetus is more grave than narcosis and in modern obstetrics a more frequent threat than trauma. In fact, it is the greatest threat which the fetus in utero faces. It is the most common cause of intrauterine death.

What can we do to forestall or at least mitigate intrauterine hypoxia? Lund has had the distinction of showing that administration of oxygen to the mother often relieves fetal

hypoxia, as evidenced by measurement of the fetal heart rate after administration of oxygen to the mother. Recently we have been following up this important observation of Dr. Lund in this manner: We have been giving alternate patients in labor oxygen during the last 5, 10, and 15 minutes before delivery; the patients are delivered under pudendal block. A similar series delivered by cesarean section has been observed in which alternate patients are given 100 per cent oxygen during the last 5, 10, and 15 minutes prior to delivery. Oxygen estimations were done in these cases on the umbilical vein blood and artery blood by a technique similar to the one described by Reid. In our control series, that is, in our patients who received no oxygen to breathe prior to delivery, the average oxygen saturation of the blood was in the neighborhood of 65 per cent—a figure that corresponds very well with that presented in the literature on the subject. By contrast, those patients who received oxygen prior to delivery showed a range of oxygen saturation from 72 to 80 per cent with the average of about 75 per cent. In other words, it is possible to elevate the oxygen saturation of the umbilical vein blood by the administration of oxygen to the mother, presumably through increasing the oxygen in the plasma, thereby diffusing more oxygen through to the fetus.

In view of these circumstances, it is our feeling that all parturients should receive oxygen during the last 5 to 10 minutes before delivery. It is true that in the great majority of cases this is not necessary, and you may object to it on the grounds that it is possible to spot cases of hypoxia by the slow fetal heart rate and single those cases out for oxygen administration. The difficulty with this policy is as follows: In the first place human fallibility enters into the picture. Although we should like to think otherwise, in the routine course of care of the parturient the fetal heart is not listened to as frequently during the last 30 minutes as one might like. Moreover, during the last few minutes the patient is draped; this does not prevent listening to the fetal heart but is perhaps a deterrent. Also, the fetal heart does show occasional vagaries in behavior; sometimes the fetal heart is quite normal in respect to rhythm and rate at the time of delivery and yet the baby shows hypoxia. On the other hand there are cases in which the fetal heart is slow and irregular and yet the baby is all right. So, although the fetal heart is a valuable index of fetal status, it is not always dependable.

For these reasons we feel that it is desirable to follow this procedure of routine oxygen administration in order to protect the welfare of the one baby in twenty who needs it and who may suffer some degree of hypoxia, although the other nineteen may not need it. The administration of oxygen to the mother in the last 5 to 15 minutes before delivery is harmless, simple, feasible, and the expense is negligible. It is our opinion that it should become part and parcel of the delivery room procedure.

DR. REID (Closing).—Dr. Montgomery calls attention to the fact that the oxygen content of the umbilical vessels is lower than the averages of previously reported studies although the arteriovenous oxygen differences are of the same magnitude of change. These, however, were all repeat elective cesarean sections. I believe Haselhorst several years ago demonstrated at cesarean section that the oxygen content of umbilical vein and artery blood was consistently higher in samples taken following a trial labor in contrast to oxygen values of fetal blood obtained at elective operation.

Dr. Huckabee of our group has shown that in ungulates the lactate-pyruvate ratio of maternal blood falls during its passage through the uterus. There is a tendency toward disappearance of the uterine arteriovenous difference during the course of the experiment and exposure of the uterus suggesting an increase in anaerobic metabolism. In this study, however, oxygen utilization remained constant throughout the thirty-minute period necessary to calculate uterine blood flow, which involved an average of six samples of uterine vein and brachial arterial blood, indicating that the exposure time of the uterus was not a determining factor.

Undoubtedly spinal anesthesia may affect uterine blood flow but the blood samples were taken only when the blood pressure was stabilized and normal. I would like to concur with Dr. Montgomery's implication of the dangers inherent in spinal anesthesia, for we regard it as the most hazardous procedure in the study.

POSTPARTUM OBSERVATION OF PELVIC TISSUE DAMAGE: FURTHER STUDIES*

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THIS report represents a review of the findings in 1,000 patients examined post partum for damage sustained in parturition. Only the findings recorded by the essayist are reported, to accomplish uniformity in clinical observations, notoriously difficult under any circumstances. The pitfalls in accuracy were recognized and hope is expressed that they are minimal.

Each patient in the group of 1,000 consecutive patients reported upon here for the first time and referred to as Series II were delivered by, or under the direction of, the author. All were delivered (by outlet or low forceps) with a right mediolateral episiotomy done at outlet station. The exceptions were 27 patients delivered by forceps rotation and 40 breech presentations, all delivered by breech assist and forceps to the aftercoming head. In all, episiotomy was done at outlet station.

A comparison will be made with 1,000 patients examined and analyzed in like manner by the essayist and reported in 1942.[1] This group is referred to as Series I. The group reported upon in 1942 were managed without forceps or episiotomy except on maternal or fetal indications. Episiotomy was done late and only when there were "signs" of impending perineal laceration. The results of the contrasting methods of management are compared.

Anatomical areas appraised for damage, with such damage recorded, are the urogenital diaphragm, the levator diaphragm, and vaginal wall attachments as manifested by detachment of the urethra, cystocele, rectocele, enterocele, detachment and prolapse of the vaginal walls. Uterine descensus and damage to the anal sphincter were also recorded.

The anterior compartment of the ischiorectal space is an area of importance damage to which was not recorded statistically, but the definite impression that it sustatined damage almost universally in Series I and only minimal damage in Series II is stated with clinical assurance.

Damage to the urogenital diaphragm was evaluated under three headings: first, the detachment of the urethra from its normal retropubic position; second, the gaping of the introitus in a state of relaxation; and third, an estimation of that portion of the urogenital diaphragm coursing between the pubic rami on each side below the introital vestibule and above the anus. For the last, 60 per cent or less of what the author estimated as normal was recorded as damage to minimize error in evaluating damage to this area.

*Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

Damage to the levator diaphragm was recorded as atrophy, determined by palpation of its components, the pubo- and the iliococcygeal muscles, by relaxation of the introitus during a voluntary effort to effect closure, and by detachment of the urethra from its retropubic attachment.

Probably the most important instances of damage are those sustained by the vaginal walls in their attachments to the endopelvic fascia on either side of the rectum. These attachments form, on either side, a roughly outlined triangular area with apices approximately at the level of the ischial spines and bases coursing along with the pubococcygeal muscles retropubically. The areas suspended figuratively or factually speaking over the rectum and beneath the bladder are subjected to permanent damage by the circumferential stretching of the vaginal tube by the passage of the fetus. Detachment of these areas, and the posterior lateral fixed areas described, is possible by overelongation of the vagina during the crowning phase of delivery. Benefit is derived from episiotomy by opening the introitus, minimizing the circumferential stretching of the vagina, thus protecting its attachments and the integrity of the vaginal wall itself.

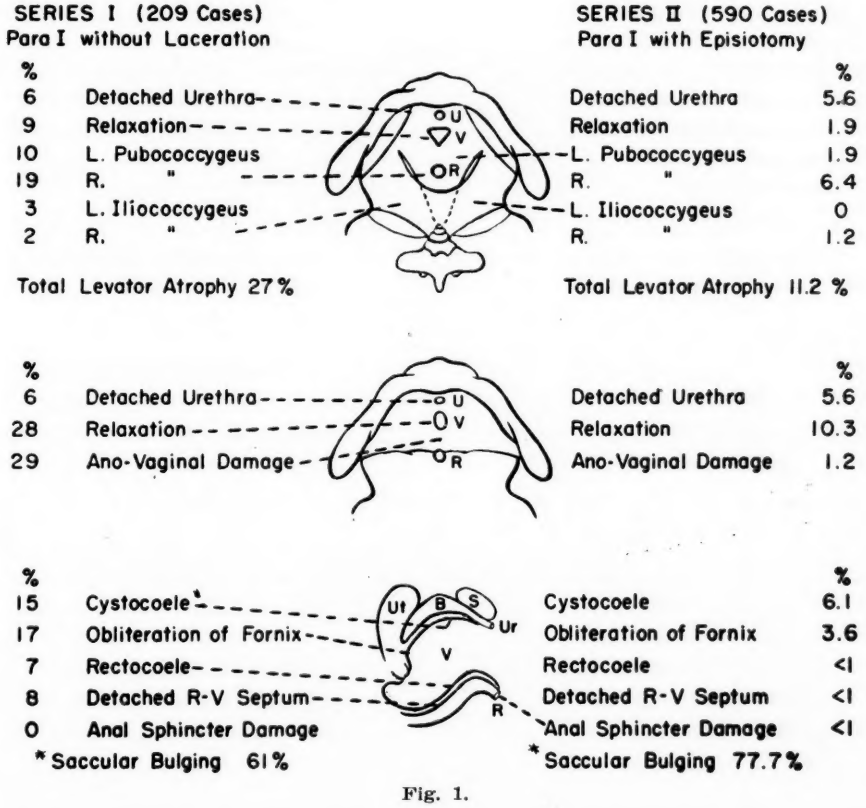

Fig. 1.

The benefit to the levator ani muscles, particularly the pubococcygeal components, by reducing overelongation of the vaginal tube is reasonable.

The urogenital diaphragm benefits directly for it is the area incised and closed by repair. Only rarely are the pubococcygeal muscles incised, and the wisdom of doing so is doubted.

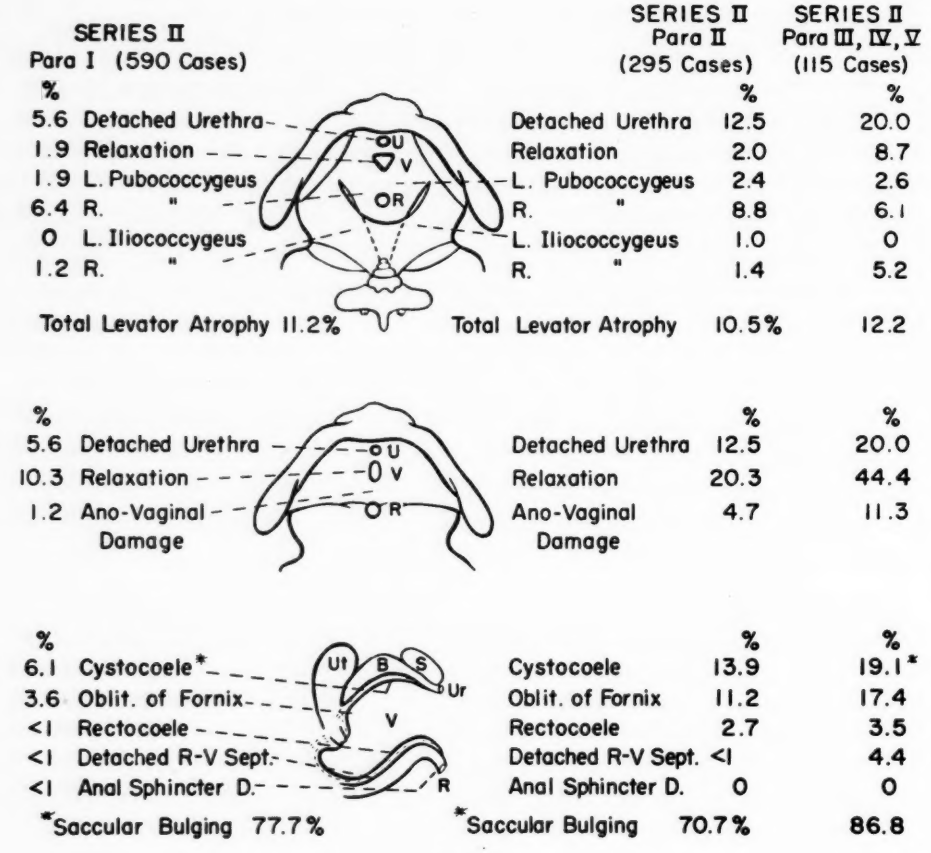

Fig. 2.

The group of 1,000 cases from the private patient service, Series II, reported for the first time, is divided into three groups:

Para i	590 cases
Para ii	295 cases
Para iii, iv, and v	115 cases

The period of time following delivery and examination varied from a minimum of two months to a maximum of 164 months, with an average of 13.73 months each. The average age of the patients was 26.81 years and the average fetal size was 3,356 grams.

The following group comparisons will be made:

1. Two hundred nine primiparas delivered spontaneously without episiotomy or laceration were compared with 590 primiparas delivered by forceps and with episiotomy. With the exception of urethral detachment, damage was greater in the group delivered spontaneously and without episiotomy (Fig. 1).

2. A group of 590 patients delivered by forceps and episiotomy in the first pregnancy were compared with a group of 295 patients of parity ii, and another group of 115 patients of parity iii, iv, and v, each of whose labors in succession had been terminated by forceps and episiotomy. These groups were compared to assess the value of repeated use of forceps and episiotomy. It will be noted that with each succeeding labor, by groups, increased damage to pelvic soft tissues occurred (Fig. 2).

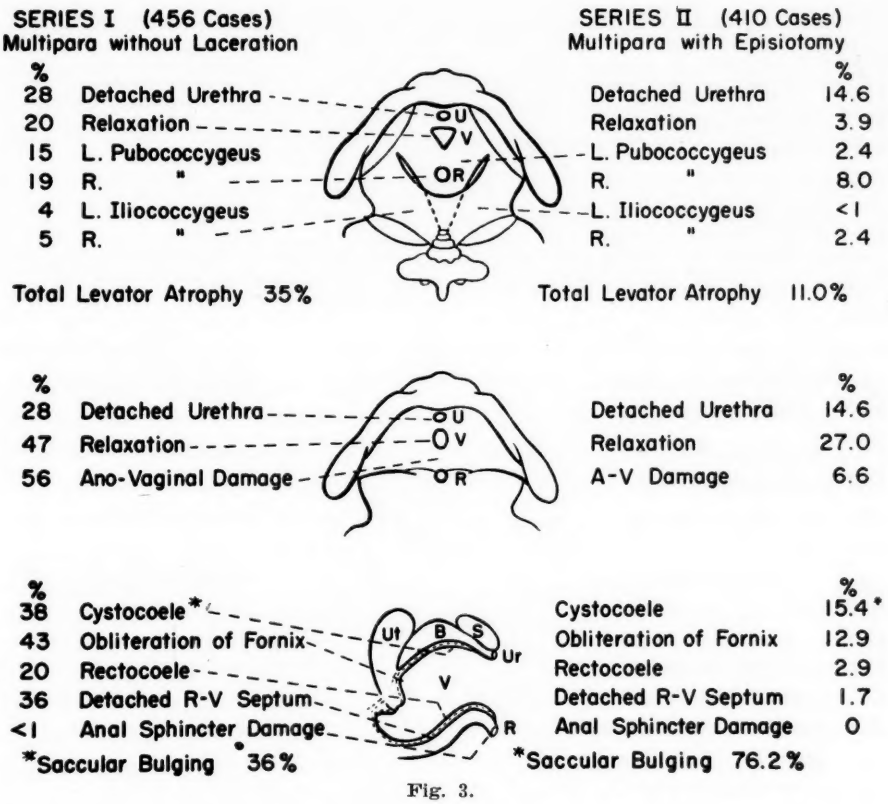

Fig. 3.

3. Four hundred fifty-six multiparous patients from Series I were compared with the foregoing 410 multiparous patients from Series II. In comparison of the two groups, the multiparous patients without operative intervention showed significant increase in damage. Individual patients manifested striking exceptions (Fig. 3).

4. A comparison was made of the 1,000 cases of Series I from the clinic service with 1,000 cases in Series II from the private patient service, showing significant difference. The patients delivered by the operative method manifested less damage (Fig. 4).

Damage to the vesical and anal sphincters was recorded as incontinence. There were 52 patients in Series I and 42 in Series II who gave a history of stress incontinence. Damage in relationship to incontinence, as evidenced by levator atrophy and urethral detachment, was reviewed with the following results:

76 patients manifested some degree of levator atrophy with no stress incontinence.
34 patients manifested the symptom with no apparent levator atrophy.
8 patients with stress incontinence had some degree of levator atrophy.

The relationship of stress incontinence to urethral detachment was reviewed in Series II with these findings:

75 patients with urethral detachment were continent.
18 patients with urethral detachment had stress incontinence.
24 patients with stress incontinence had what was interpreted on physical examination as normal urethral pubic relationships.

Present knowledge of the physiology of micturition may allow these inconsistencies.

The incidence of uterine descensus was 9 in Series I, one being complete, while in Series II there were 26 cases, all of first degree. There is no apparent explanation for the disparity. No studies other than physical examinations were done.

Five patients in Series I sustained damage to the anal sphincter with immediate satisfactory results from repair.

One patient in Series II sustained anal sphincter damage associated with partial incontinence for twelve months. No enteroceles were recognized in either group.

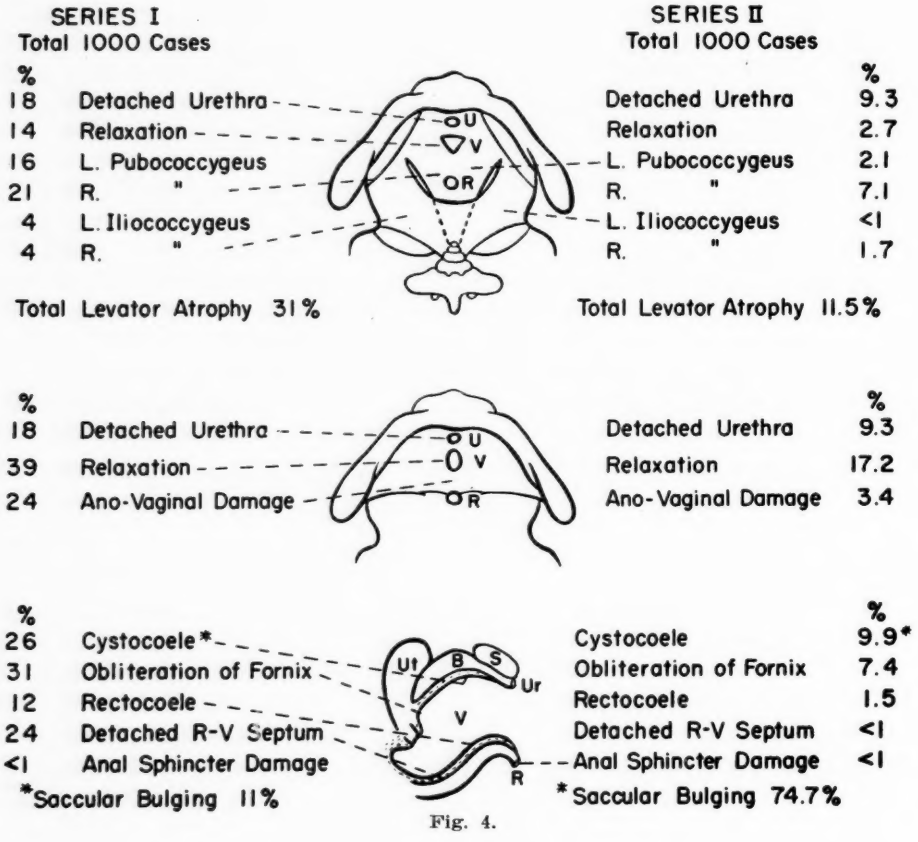

Fig. 4.

Comment

Damage to pelvic tissues resulting from parturition has been evaluated objectively from pelvic examination and the symptom of incontinence, vesical and anal.

The vagina is most vulnerable to injury, with sequelae capable of producing disability. Detachment of the vagina from its retropubic attachments, associated with descent of the urethra and neck of the bladder, is probably the most critical injury. The detachment of the retropubic attachments of the vagina, recorded as urethral detachment, when associated with detachment of the anterior subvesical portion of the vagina from its endopelvic fascial

attachments laterally, and from the cervix and parametrial attachments at the anterior and lateral fornices, may over a long period of time progress to cystourethrocele alone, or to uterovaginal prolapse with or without elongation of the cervix. Saccular bulging of the anterior vaginal wall, classified as saccular cystocele, undoubtedly results from damage to the vaginal wall per se from overdistention of the vaginal tube; the same is true of rectocele posteriorly. The detachment of the posterior vaginal wall on either side of the rectum may lead to diffuse bulging of this area without true rectocele, but when combined with damage to other areas this will predispose to uterovaginal prolapse.

From the data presented and a comparison of the two series, significant protection to the vagina by episiotomy is shown. The increasing damage revealed in multiparas may be due to delay in time of episiotomy but the effect of repeated pregnancy itself undoubtedly plays a part. The rapidity of the second stage of labor, not permitting retraction and the completion of the normal uterovaginal mechanism, may predispose to detachment of the vaginal wall in the labors of multiparous patients.

Damage to the levator ani muscles was reported in two specific categories, the first as relaxation and the second as atrophy. Relaxation was interpreted as present when on palpation the muscles were intact but there was inability to accomplish effective contraction. Exercise will benefit a large number in this group. Atrophy represented loss of muscle with a characteristic defect. This defect is replacement by ischiorectal fat and scar tissue. No constant symptom complex was related and the damage is irreparable. Benefit to this area associated with episiotomy was not explained by incision and repair of the muscles and only rarely did the episiotomy extend to include the levators.

The urogenital diaphragm was appraised more objectively and the benefit from episiotomy is more obvious as it was incised and repaired in each case.

From the data presented benefit by episiotomy to maternal soft tissue is demonstrated.

Reference

1. Gainey, Harold L.: Am. J. Obst. & Gynec. **45**: 457, 1943.

Discussion

DR. CLYDE L. RANDALL, Buffalo, N. Y.—At least two points deserve emphasis. So far as I know, this is the first really objective demonstration of the value of episiotomy. Second, we should recognize the importance of differentiating changes due to true relaxation from the appearance suggesting relaxation, but actually due to injury and resulting atrophy. It is evident that Kegal's exercises cannot be expected to improve the situation when atrophy rather than relaxation accounts for discomfort or dysfunction.

Perhaps most important, however, is the demonstration of a method by which any one of us may add to our knowledge concerning the effects of parturition on the soft tissues of the maternal pelvis. Reliable and definite data have been needed. The factual information offered in this report might well replace the unreliable "impressions" with which we have too long seemed satisfied. Incorporation of a chart to record the type of data suggested at the time the patient is examined four, six, or eight weeks, and again at six months following delivery would involve little change in our usual routine and would quickly provide an improved appraisal of the patient's postpartum condition.

In 1942 when Dr. Gainey first presented observations regarding soft-tissue damage after spontaneous delivery the value of such an objective study seemed evident. Now the value of that early report has been increased and it is obvious that the recording of such definite data provides an important means of evaluating different techniques of conducting labor and delivery.

Dr. Gainey has stated that the most important areas of damage are the vaginal walls in their attachment to the endopelvic fascia on either side of the rectum. Varying degrees of detachment are possible by overelongation of the vagina during the crowning phase of delivery. The benefit derived from episiotomy is accomplished by opening the introitus, minimizing the elongation or stretching as well as the distention of the vagina, thus protecting its attachments as well as the integrity of the vaginal membrane itself.

With this postpartum appraisal of soft tissue injury in mind, several years ago I decided that if we were to employ episiotomy routinely in an effort to reduce the elongation and overstretching of the vagina, a deep midline incision done before the vertex distends the perineum should accomplish more "preservation" than the mediolateral episiotomy employed by the author, particularly should the mediolateral opening be made after "crowning" begins. No doubt there are others in this audience who feel that variations in the techniques indicated might result in even less damage than has been reported today, but the relative merits of different types of episiotomy or the advantages of a particular type of anesthesia, like the virtues of your favorite forceps, are not matters for discussion at this time. It is the method of evaluating soft-tissue damage and the value of such observations when made in systematic fashion that we should recognize.

I cannot resist the temptation, however, to turn your attention momentarily toward another result of labor that we must also keep in mind.

Dr. Gainey has restricted his discussion to a consideration of the soft-tissue damage chargeable to the forces of parturition. It is evident to all, however, that if we are to evaluate the routine employment of episiotomy and the purely elective use of low or outlet forceps, we should not forget the other advantages DeLee originally claimed for "prophylactic" forceps. Today, thirty years after DeLee's original reports, little search would be necessary to find data illustrating the advantages to the baby of employing episiotomy and forceps to shorten the second stage of labor.

For instance, in each of seven hospitals in the city of Buffalo, the fetal loss associated with each type of delivery has been carefully tabulated since January, 1945. During the ten-year period recently surveyed, 38,932 deliveries had terminated spontaneously and 110,335 infants were delivered by low or outlet forceps. "Corrected" rates, excluding all losses due to antepartum fetal death and the loss of infants weighing less than 1,500 grams at birth, also omitted those born with congenital defects incompatible with extrauterine life. Baetz has reported that the thus "corrected" rates of perinatal mortality average 15.4 babies lost per 1,000 spontaneous births compared to 7.2 fetal deaths per each 1,000 births terminated by outlet forceps.

In such figures, as in the data reported by Dr. Gainey today, there seems convincing evidence that good obstetrical practice can realize better results than those usually attained by normal, spontaneous childbirth.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—In 1942 I discussed Dr. Gainey's first paper on this subject. At that time I was impressed, as I am today, with the meticulous fashion in which the patients were analyzed and the results classified and reported.

The addition of data concerning the end results of episiotomy which has been presented today by Dr. Gainey is a natural sequence to these previous studies, for episiotomy in this country is so commonly employed that it may be considered a part of our normal obstetrics. Episiotomy, as performed and repaired by obstetricians who understand the anatomy of this area and the technique of plastic repair, is a refinement of the American

obstetrics which has resulted in far better end results for the American mother and has decreased the frequency of gynecologic procedures and plastic repairs which have to be performed later in life.

I would like to believe that the good results which Dr. Gainey has reported today are the result of episiotomy and repair per se and are not necessarily related to the frequent forceps deliveries which in his hands have accompanied this procedure. In my own practice I find no reason to believe that the use of low or "prophylactic" forceps combined with episiotomy gives a better result than spontaneous delivery with episiotomy.

It would be unfortunate if this paper and its discussion went out carrying the impression that it is the universal opinion of the members of this society that low forceps delivery with episiotomy is the method of choice in vaginal delivery. This question of the efficacy or advisability of delivery by forceps is a matter which requires more thorough consideration than can be given in this brief discussion.

DR. GAINEY (by invitation) (Closing).—I would like to support Dr. Montgomery's statement. If it were possible, and I hope it will be at some time in the future, to analyze a group of patients delivered by operative obstetrics, we might be able to show that there is a marked increase in damage by the use of forceps and episiotomy done on an operative basis. I think that is important to emphasize. We have those observations but we do not have details enough yet to make an evaluation of the situation. Our own choice and philosophy are in favor of conservative obstetrics, and will continue to be so. Any interpretation of this report as supporting operative obstetrics is wrong. This is an attempt to compare one philosophy of obstetrics with another as objectively as possible, the one of spontaneous expulsion of the fetus and episiotomy only on impending laceration, and the other of the use of forceps as termed over the years "prophylactic," with episiotomy done routinely to protect maternal soft tissue. The latter has received widespread acceptance and extensive use in many teaching centers.

THE SIGNIFICANCE OF BASAL-CELL HYPERACTIVITY IN CERVICAL BIOPSIES*

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(From the Gynecological Department of the Johns Hopkins University and Hospital)

THE relatively recent realization that carcinoma of the uterine cervix might be detected in its asymptomatic, noninvasive stage has prompted widespread sampling of the clinically benign cervix. The histological examination of these biopsies has revealed some phases of cervical epithelium which while not manifestly benign yet do not satisfy the criteria of malignancy. These epithelial aberrations have been designated by a variety of terms such as "anaplasia," "dysplasia," "simple atypical epithelium," "increasingly atypical epithelium," "atypical hyperplasia," "basal-cell hyperactivity," and others. All of these terms have been employed to depict essentially the same histological picture. The significance of this microscopic finding and, particularly, its possible relationship to carcinoma in situ have perplexed the minds of all serious students of cervical histopathology and have stimulated this investigation.

The term "basal-cell hyperactivity" is used throughout this thesis, neither because we feel it is most descriptive of this lesion nor that it enjoys any particular superiority over other nomenclature, but merely because since 1940 in our laboratory this epithelial abnormality has been designated thus. We have applied this term to that histological picture in which we find an epithelial layer which approximates in thickness that of the normal portio vaginalis and in which we find an abnormal number of immature cells so that normal stratification is interfered with and normal architecture is partially destroyed. We find all degrees of this epithelial deviation, depending upon the number and anaplasia of the immature cells and varying from slight alterations in the normal surface epithelium to a picture simulating carcinoma in situ. To facilitate classification and comparison, in this study we have arbitrarily divided basal-cell hyperactivity into three stages in which Stage I (Fig. 1) shows only slight divergence from the normal epithelial layer, Stage II (Fig. 2) represents more conspicuous changes, while Stage III (Fig. 3) approaches the microscopic picture of surface carcinoma.

Unfortunately, at the present time there is no unanimity of opinion as to the histological criteria of carcinoma in situ. The diagnosis of this lesion thus far has resisted objective standards and remains a subjective one requiring of the microscopist considerable experience in cervical histopathology. In this

*Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

study the diagnosis of carcinoma in situ has been accepted only when the epithelial layer equals the thickness of that of the normal portio vaginalis, when all the cells comprising that layer have the characteristics of malignancy, when there is complete loss of stratification, and when the underlying basement membrane is intact (Fig. 4).

The material for our investigation was assembled from the gynecological outpatient clinic of the Johns Hopkins Hospital during a four-year period terminating in December, 1954. During this time there were 5,054 initial visits and 47,509 return visits of a group of predominantly Negro patients. Cervical biopsies, although obtained quite freely, were by no means a routine procedure and were obtained only when signs or symptoms aroused the suspicion of cervical abnormality. The Gayler punch biopsy clamp was employed to obtain tissue at the squamocolumnar junction from each of the four quadrants of the cervix. From this group of patients, 7,553 biopsies were submitted for histological examination. Those patients in whom the diagnosis of basal-cell hyperactivity was entertained were immediately referred to a special follow-up clinic for more thorough investigation of the cervix. Here the patients were kept under observation with periodic cervical biopsies until either the cervical epithelium appeared to return to normal on the basis of repeated negative biopsies or the patient was proved to have carcinoma in situ when definitive therapy was instituted. Thus the period of study of the individual patients varied from a few months to four years.

Cytological smears were obtained in conjunction with practically all biopsies as well as independently. In general, there was close agreement between the cytological and histological picture and the smear often was found useful in prompting the taking of a biopsy. In this study, however, we have made no attempt specifically to evaluate the cytological findings.

Initially, 343 patients with a diagnosis of basal-cell hyperactivity were referred to us for further evaluation. However, review of these original biopsies disclosed that the histological changes in 101 cases were insufficient to justify such a diagnosis, in 20 cases the changes were sufficiently marked to meet our criteria for the diagnosis of carcinoma in situ, and in 7 there was actual invasion of the stroma by malignant cells. These cases were immediately excluded from our study, as well as an additional 24 cases in which the follow-up investigation is inadequate. Thus 191 patients in whom the initial cervical biopsy showed definite basal-cell hyperactivity and whose subsequent investigation permits appraisal comprise the material of this study (Table I).

TABLE I. MATERIAL

Patients referred to clinic		343
Insufficient histological changes	101	
Carcinoma in situ	20	
Invasive carcinoma	7	
Insufficient observation	24	
Patients included in study		191

Classification of these 191 patients according to the degree of basal-cell hyperactivity noted in the original biopsy placed 93 in Stage I, 63 in Stage II, and 35 in Stage III (Table II). Evaluation of these groups in accordance with their subsequent study may be conveniently effected by referring to the individual cases as having shown "regression," "no change," or "progression" of the epithelial abnormality, noting in particular those cases in which the diagnosis of carcinoma in situ was eventually established.

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Stage I basal-cell hyperactivity, showing minimal increase in abnormal nuclei in the basal layer. Normal stratification has not been disturbed.

Fig. 2.—Stage II basal-cell hyperactivity, with increase in atypical cells. There is some alteration in normal stratification.

Fig. 3.—Stage III basal-cell hyperactivity exhibiting marked increase in number of atypical cells and marked disturbance of normal stratification.

TABLE II. CLASSIFICATION AND SUBSEQUENT FINDINGS ACCORDING TO STAGE OF BASAL-CELL HYPERACTIVITY FOUND IN ORIGINAL BIOPSY

STAGE OF B. C. H.	I	II	III
Number of cases	93	63	35
Regression	50	28	6
No change	28	20	6
Progression	15	15	23
Carcinoma in situ	2 (2%)	8 (11%)	23 (65%)

Of the 93 patients in Stage I in whom the initial biopsy possessed only a minor degree of basal-cell hyperactivity, further observation with periodic cervical biopsies disclosed that eventually 50 reverted to normal cervical epithelium, 28 persisted with the same degree of hyperactivity, while 15 showed an apparent progress to a greater degree of hyperactivity but thus far in only 2, or 2.1 per cent, did further study show a carcinoma in situ.

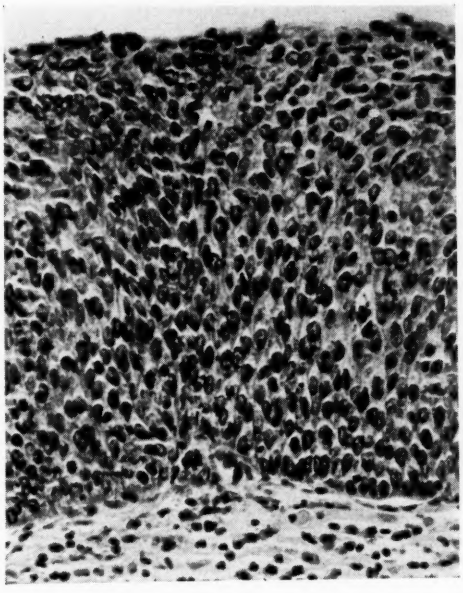

Fig. 4.—Carcinoma in situ. The entire thickness of the surface epithelium is composed of abnormal cells and there is complete loss of stratification.

Further study of the 63 patients in whom the original biopsy exhibited a moderate degree of basal-cell hyperactivity disclosed that 28 of these regressed, 20 experienced no essential change, while 15 apparently progressed to a greater degree of epithelial abnormality, including 8, or 11 per cent, in whom the diagnosis of carcinoma in situ has been confirmed. Among the 35 patients initially classified as possessing a marked degree of basal-cell hyperactivity, continued observation indicated that 6 cases regressed, 6 thus far have shown no change, while in 23, or 65 per cent, subsequent biopsies satisfied our criteria of carcinoma in situ.

From the clinical aspect we are particularly interested in what, if any, relationship basal-cell hyperactivity bears to carcinoma in situ of the uterine cervix. Hence, a more critical inquiry into those cases in which the initial cervical biopsy showed only some degree of epithelial hyperactivity but subsequent biopsies possessed the characteristics of surface carcinoma is essential.

In our study there are 33 such cases. In 2 of these the initial biopsy possessed only a minor degree of basal-cell hyperactivity and were classified as Stage I; in 8 the original epithelial abnormality was thought to be moderate and was placed in Stage II, while in 23 the hyperactivity of the surface epithelium was adjudged to be marked and thus fell into Stage III (Table III). Further analysis of the group of patients showed that they were observed for a period varying between 2 and 48 months and that the number of cervical biopsies taken on the individual patients varied between 3 and 10 (Table IV),

TABLE III. CASES IN WHICH CARCINOMA IN SITU WAS ULTIMATELY DIAGNOSED

Stage I basal-cell hyperactivity	2
Stage II basal-cell hyperactivity	8
Stage III basal-cell hyperactivity	23
Total	33

TABLE IV. ANALYSIS OF CASES IN WHICH CARCINOMA IN SITU WAS ULTIMATELY DIAGNOSED

CASE NO.	STAGE OF BASAL-CELL HYPERACTIVITY	MONTHS OBSERVED	NO. OF BIOPSIES
245	I	22	10
359	I	16	7
15	II	24	3
44	II	39	3
84	II	4	5
173	II	8	5
237	II	5	4
269	II	48	9
315	II	7	3
340	II	26	8
92	III	2	4
174	III	2	3
182	III	36	5
183	III	6	5
187	III	6	4
177	III	2	3
192	III	4	3
193	III	2	4
195	III	4	6
206	III	2	4
208	III	2	3
213	III	2	3
221	III	4	4
223	III	2	4
229	III	2	3
225	III	20	9
226	III	12	6
194	III	39	8
196	III	17	6
231	III	7	4
232	III	3	5
240	III	2	5
249	III	18	5

Since we know that basal-cell hyperactivity and carcinoma in situ occur in the same cervix and at the same time it is quite possible that in the majority of these 33 cases the conditions existed simultaneously and that the final diagnosis of carcinoma in situ does not necessarily represent a progression of the basal-cell hyperactivity. In order to diminish the likelihood of this coincidence we might consider of these 33 cases only those which were observed

for more than 16 months. With this reduction we are left with a residue of 11 cases of the original group of 195 cases in which the possibility of a progression of basal-cell hyperactivity to carcinoma in situ must be considered.

In 2 of these 11 cases the original biopsy was classified as Stage I basal-cell hyperactivity, 4 were initially placed into Stage II, and 5 into Stage III. These 11 cases were kept under observation for periods varying between 16 and 48 months during which period 3 to 10 biopsies were obtained from each cervix (Table V). Consideration of this select group of cases, observed over a relatively long period of time with ample periodic sampling of the cervical epithelium, would seem to imply that basal-cell hyperactivity may progress to carcinoma in situ.

TABLE V. ANALYSIS OF CASES WHICH TEND TO SHOW A PROGRESSION OF BASAL-CELL HYPERACTIVITY TO CARCINOMA IN SITU

CASE NO.	STAGE OF BASAL-CELL HYPERACTIVITY	MONTHS OBSERVED	NO. OF BIOPSIES
245	I	22	10
359	I	16	7
15	II	24	3
44	II	30	3
269	II	48	9
340	II	26	8
182	III	36	5
194	III	39	8
196	III	17	6
249	III	18	5
225	III	20	9

The following cases selected from this group are presented in some detail, documented with appropriate photomicrographs:

CASE 269.—This 42-year-old multiparous Negro woman was first seen Oct. 20, 1950, complaining of profuse and prolonged menses for the previous five months. The cervix was found to be enlarged and lacerated. In general, however, the mucosa was smooth and intact save for a narrow area of "erosion" around the entire external os. The uterus was enlarged and irregular while the adnexa were normal to palpation. Curettage of the fundus and biopsy of the cervix were carried out on Dec. 2, 1950. The endometrium presented no abnormality but the cervical biopsy showed basal-cell hyperactivity which we classified as Stage II (Fig. 5, *A*). The cervix was rebiopsied on 6 occasions during the following three and one-half years and the degree of epithelial abnormality remained unchanged (Fig. 5, *B*). On Sept. 16, 1954, the biopsy showed more striking atypicalities (Fig. 5, *C*) and repeat biopsy on Dec. 16, 1954 (Fig. 5, *D*), showed histological changes sufficient to justify the diagnosis of carcinoma in situ.

CASE 359.—A 42-year-old white woman was seen originally in September, 1953, complaining of lower abdominal discomfort. History disclosed that she had had 2 full-term pregnancies and no abnormal vaginal bleeding. The cervix was described as being hypertrophied with a deep laceration, the edge of which was raw and bled when irritated. Cervical biopsy at this time revealed basal-cell hyperplasia classified as Stage I (Fig. 6, *A*). During the next seven months, 4 additional biopsies showed no change in this picture. The biopsy obtained eleven months later (Fig. 6, *B*) showed some progression of the epithelial abnormality; that obtained fifteen months later showed even more striking changes (Fig. 6, *C*) while the biopsy taken sixteen months later was interpreted as carcinoma in situ (Fig. 6, *D*).

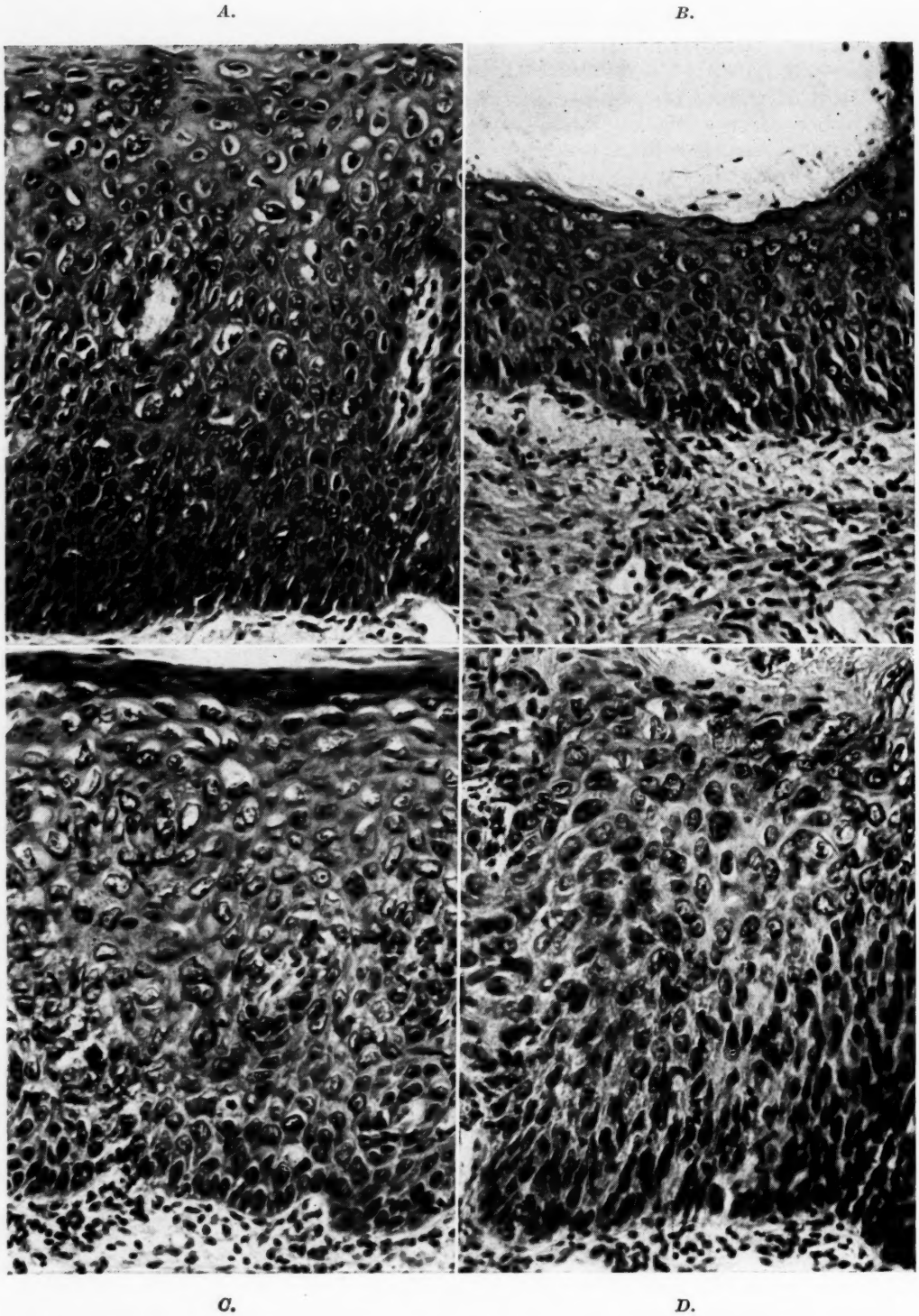

Fig. 5.—(Case 269.) *A*, Biopsy obtained Dec. 2, 1950, showing Stage II basal-cell hyperactivity.

B, Biopsy obtained May 3, 1951, again showing Stage II basal-cell hyperactivity.

C, Biopsy obtained Sept. 16, 1954, showing Stage III basal-cell hyperactivity.

D, Biopsy obtained Dec. 16, 1954, diagnosed as carcinoma in situ.

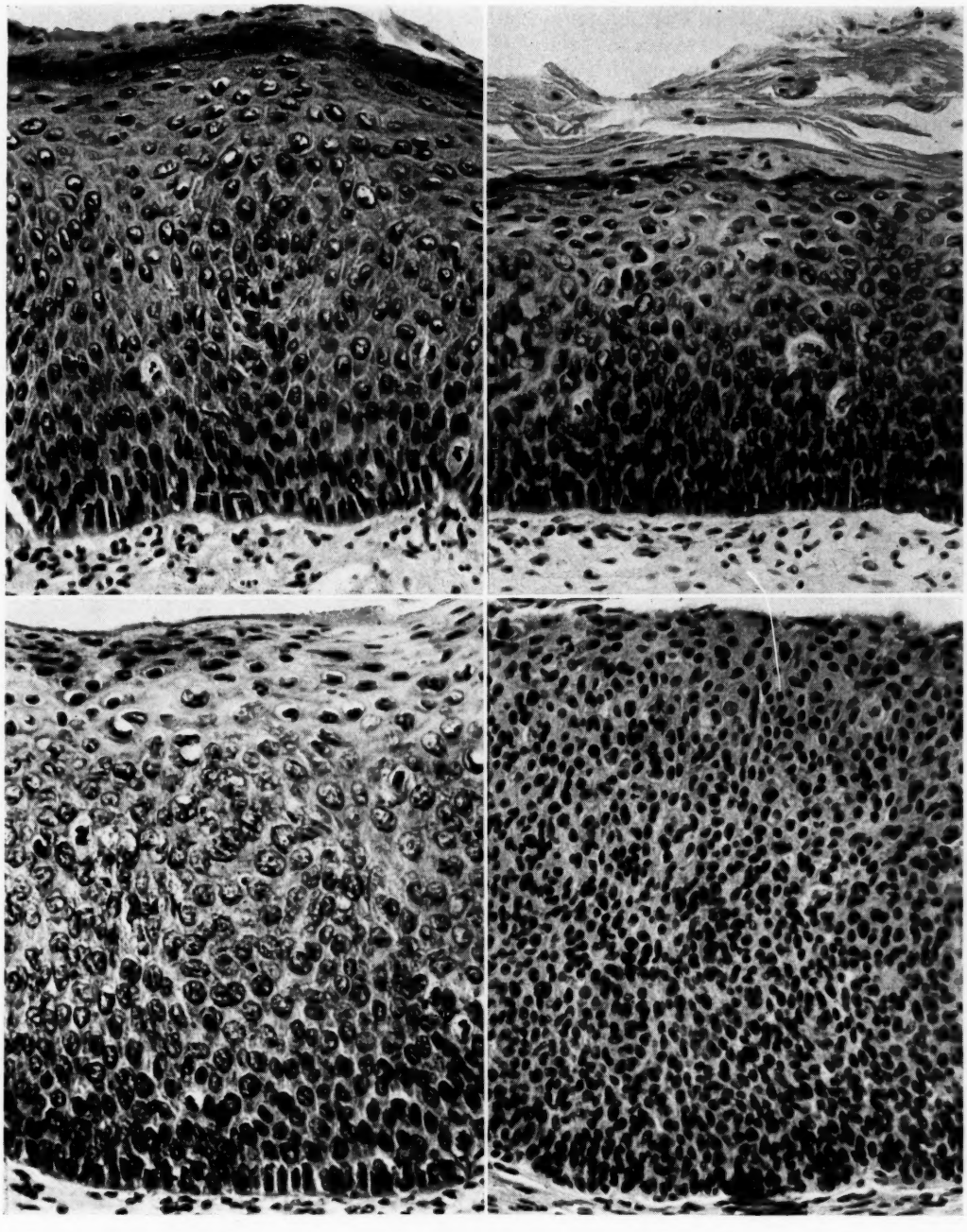

Fig. 6.—(Case 359.) *A*, Biopsy taken Oct. 2, 1953, showing Stage I basal-cell hyperactivity.

B, Biopsy taken Sept. 26, 1954, showing Stage II basal-cell hyperactivity.

C, Biopsy taken Dec. 30, 1954, showing Stage III basal-cell hyperactivity.

D, Biopsy taken Jan. 25, 1955, diagnosed as carcinoma in situ.

Of equal significance are the 6 cases in which the initial biopsy showed a degree of basal-cell hyperactivity sufficient for us to classify them as Stage III but in which subsequent biopsies failed to show any epithelial abnormality. These cases in general have been followed for a shorter period of time, the longest twenty-four months (Table VI). The follow-up biopsies, however, have been so consistently negative that it is most unlikely that these cervices at the present harbor any epithelial abnormality. Exemplifying this group of cases is the cervical biopsy (Fig. 7) obtained on March 28, 1951, from a 41-year-old white woman who complained of menorrhagia and whose cervix contained no grossly visible lesion. A second biopsy obtained two weeks later showed the same histological picture, yet 5 subsequent biopsies taken during the next twenty-three months were negative. As another example, Fig. 8 shows an area of marked basal-cell hyperactivity taken from the "eroded" cervix of a 28-year-old Negro woman who complained of a profuse vaginal discharge. This same cervix was rebiopsied on 6 occasions during the succeeding seven months but showed no subsequent epithelial abnormality. These cases should impress upon us the fact that even marked atypicalities are reversible.

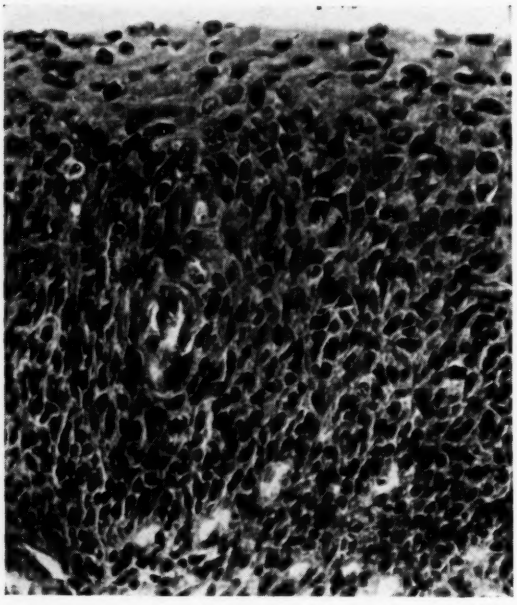

Fig. 7.

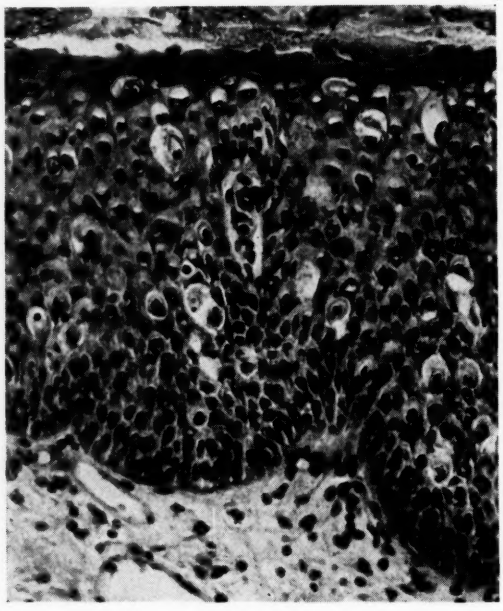

Fig. 8.

Fig. 7.—(Case 210.) Biopsy of March 28, 1951, showing rather marked basal-cell hyperactivity. Same histological picture found in biopsy taken two weeks later; however, five subsequent biopsies taken during next two years were negative.

Fig. 8.—(Case 109.) Cervical biopsy of Nov. 25, 1952, exhibiting striking atypicality of surface epithelium, yet six biopsies obtained during next nine months showed no abnormality.

TABLE VI. CASES OF STAGE III BASAL-CELL HYPERACTIVITY WHICH SHOWED COMPLETE REGRESSION

CASE NO.	TIME OBSERVED	NO. OF BIOPSIES
31	3 months	3
81	6 months	4
109	9 months	7
204	19 months	4
210	24 months	7
259	4 months	5

Comment

In evaluating this study of the significance of basal-cell hyperactivity in cervical biopsies certain deficiencies inherent in such an investigation must be recognized:

1. The punch biopsy allows us to assay only that small segment of cervical tissue removed and fails to give us any information concerning the remaining portion of the cervix. In juxtaposition to an area of basal-cell hyperactivity we may have a carcinoma in situ or even invasive cancer. Conceivably, also, the entire area of epithelial abnormality could be completely removed by the biopsy clamp.

2. Available knowledge concerning the noninvasive stage of cervical cancers warns us that substantial conclusions relating to the ultimate fate of abnormal cervical epithelium require observation over a period of years rather than months. While this study has been conducted over a term of four years, the majority of the cases have been observed for little more than two years.

3. The evaluation of abnormal cervical epithelium including the diagnosis of carcinoma in situ is an extremely subjective one. In this study in order to decrease the personal inconsistencies to a minimum all evaluations have been made by one person using the depicted "stages" as his guide in evaluating the degree of basal-cell hyperactivity.

Conclusions

Conscious of these limitations we venture to make the following observations derived from this investigation:

1. Basal-cell hyperactivity when found in cervical biopsies requires more thorough investigation of the cervix as carcinoma in situ will be found eventually in a substantial number of these cases. In our study noninvasive cancer was found in 33, or 17 per cent, of the 197 cases investigated.

2. The probability of this eventuality increases sharply with the degree of basal-cell hyperactivity. While only 2 per cent of those cases classified by us as showing Stage I basal-cell hyperactivity were eventually proved to be carcinoma in situ, 65 per cent of those in Stage III finally showed this histological picture.

3. Evaluation of a selected group of 11 of our cases seems to indicate that basal-cell hyperactivity may actually progress to carcinoma in situ.

4. Observation of complete regression of even a marked degree of basal-cell hyperactivity warns us that this condition must be differentiated from carcinoma in situ and never be diagnosed or treated as such.

Discussion

DR. ROGER B. SCOTT, Cleveland, Ohio.—Dr. Galvin over the past fifteen years has made a very intensive study of carcinoma in situ of the cervix. This present report is valuable for it represents the personal opinion of epithelial alterations as interpreted by one individual who has followed strict criteria. For example, he has realized that some of the surface epithelium might be missing from the stained sections and is unwilling to make the diagnosis of "basal-cell hyperactivity" unless the epithelial layer approximates

in thickness that of the normal portio vaginalis. The 33 patients who were proved to have carcinoma in situ subsequently were subjected to a total of 162 biopsy studies! A real skeptic, who believes that trauma is an important etiological factor in the development of carcinoma of the cervix, might even accuse Dr. Galvin of producing these lesions with his biopsy forceps.

Dr. Galvin lost only 24 patients out of a total of 343. This is even more impressive when it is realized that the vast majority of these patients are Negro and partially indigent.

The classification of these changes into Stages I, II, and III might lead to some confusion, since the word stage is used so frequently in determining the extent of cancers of the cervix. Grade or degree might be a better term. Most of us have observed epithelial changes, particularly of the minor type, in association with vaginitis. Does Dr. Galvin have any information on the presence or absence of associated vaginitis in his group of patients? How many of these patients were pregnant at some time during this study? How does the mean age of this group compare with the mean age in his series of carcinoma in situ?

Drs. Reagan and Hicks and I have recently reported on a smaller series of these lesions. Sixty-five patients with atypical hyperplasia of the cervix (not an ideal term but one which we prefer to basal-cell hyperactivity) at University Hospitals of Cleveland were followed for one and one-half to four years. In 35 women the changes either regressed or were not demonstrable on subsequent examinations, while in 20 the changes had persisted as judged by biopsies and cell studies. An interpretation of carcinoma in situ was made in 9 patients and one patient developed invasive cancer.

The most serious deficiency in evaluation of this study is one which Dr. Galvin has stressed. The punch biopsy assays only a small portion of the cervix and there is no assurance that these lesser epithelial changes may not be adjacent to a carcinoma in situ or an invasive cancer. To circumvent this deficiency we have placed a heavy responsibility upon our very capable cytologist and pathologist, Dr. James W. Reagan. We follow our patients by cytology and occasional punch biopsy *until* the cytology studies reveal changes compatible with carcinoma in situ, as determined by the number of altered cells and the magnitude of this alteration. At this point a wide and deep sharp conization is done and all of this tissue is step-sectioned. In a group of 100 patients with carcinoma in situ of the cervix, where the complete cervix was available for study, we found the major epithelial alteration within the canal in 90 patients and only in 10 patients was there extension of this lesion out on the portio. If our findings are valid, then punch biopsies of the portio would miss the area of major epithelial alteration in the vast majority of instances. How can Dr. Galvin say with any degree of assurance that 7 of the 35 cases of "Stage III basal-cell hyperactivity" completely regressed when only punch biopsies are used and when the follow-up period of these 7 patients is only three to twenty-four months? A greater use of cytology, fewer punch biopsies, and delayed definitive biopsy by sharp conization is another way to approach such a study as Dr. Galvin has made.

A recent patient in our study has impressed us with the strong probability that atypical hyperplasia can eventuate in carcinoma in situ. A 55-year-old woman (A. M., Hist. No. 246-299) had a sharp conization on May 9, 1951, because atypical hyperplasia was suspected by cytology studies. Complete step-sectioning of the cervical cone specimen revealed only a minimal degree of atypical hyperplasia. Over the following three years and seven months she was followed by ten cytologic studies. These were negative or showed only minor changes until one month before hysterectomy was done. The last cytology report was as follows: "Cellular changes consistent with carcinoma in situ, although atypical hyperplasia is present." On Dec. 1, 1954, a wide, total abdominal hysterectomy was done together with a bilateral salpingo-oophorectomy. The regenerated squamous epithelium of the cervical canal showed atypical hyperplasia (Figs. 1 and 2) and carcinoma in situ was found high in the cervical canal, involving glands (Figs. 3 and 4). This carcinoma in situ may have been in this location at the time of the sharp

conization; it seems most likely, however, that an area of atypical hyperplasia remaining in the small portion of the upper cervical canal progressed to a carcinoma in situ over the period of three years and seven months.

Fig. 1.

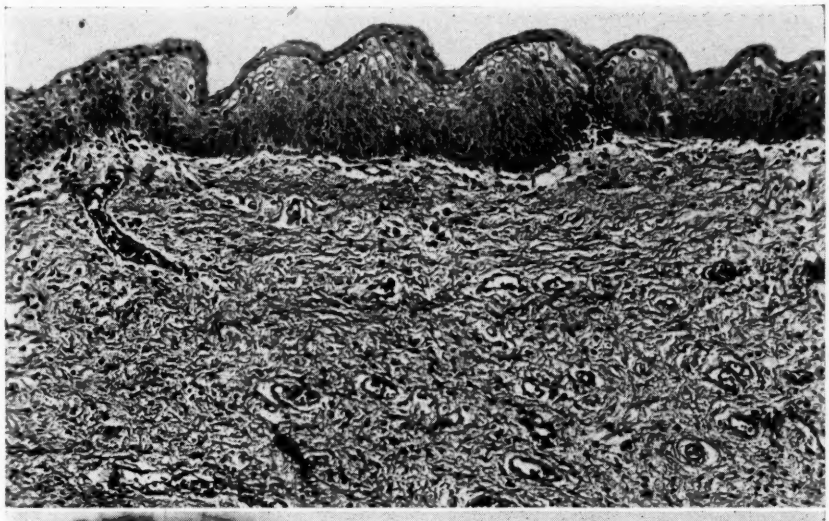

Fig. 2.

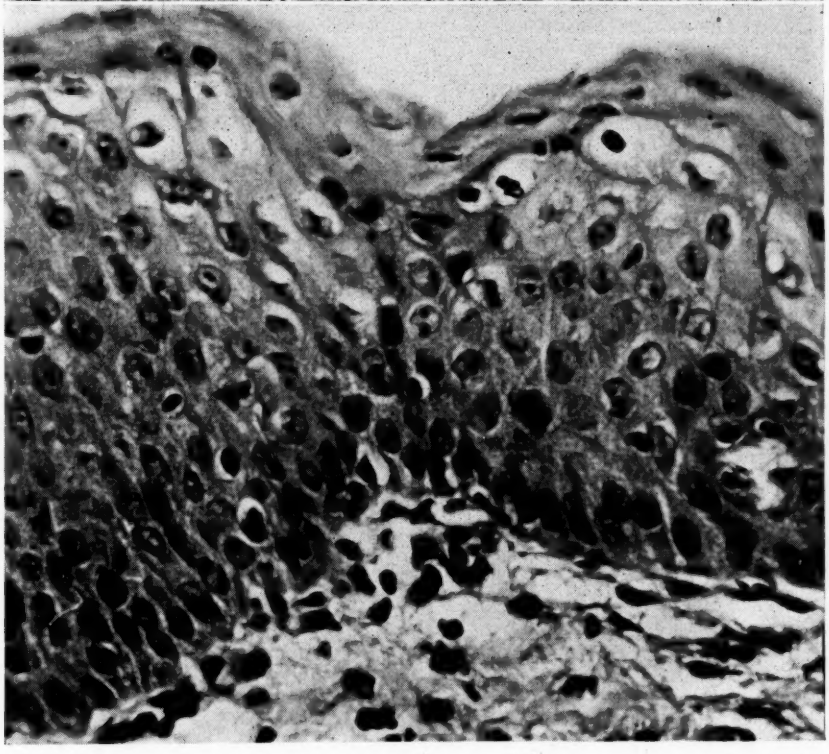

Fig. 1.—Regenerated epithelium of the cervical canal three years and seven months after a sharp conization. Note the parakeratosis and the moderate alteration of the cells in the lower layers of the epithelium. These alterations are more marked than those found in the previously removed cone. (×100.)

Fig. 2.—High-power study of an area in Fig. 1. (×500.)

Fig. 3.

Fig. 4.

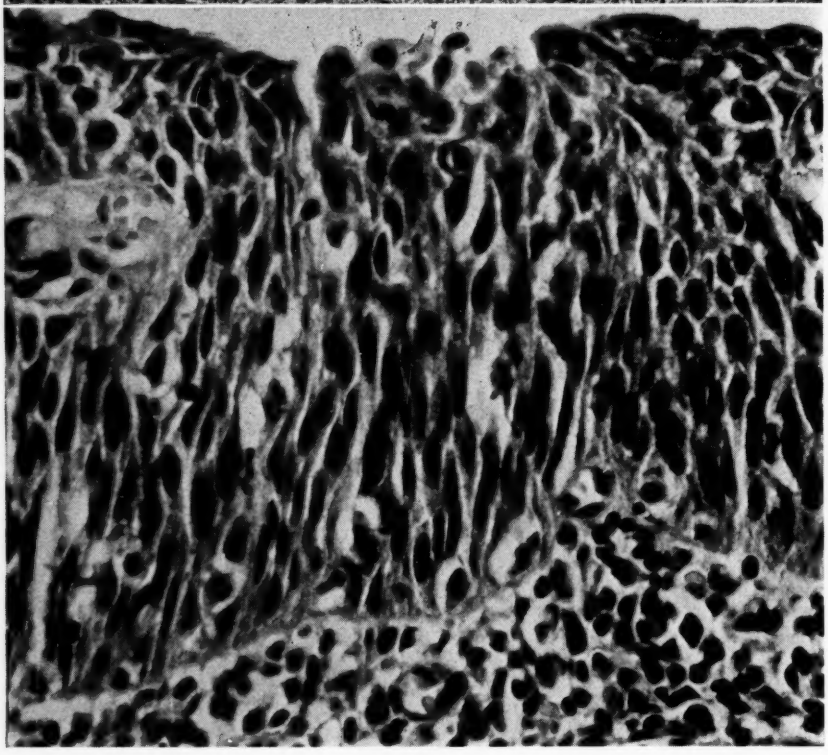

Fig. 3.—Area of carcinoma in situ in the upper border of the cervical canal three years and seven months after a sharp conization of the cervix for atypical hyperplasia. (×50.)

Fig. 4.—High power of area in Fig. 3 showing cellular alterations involving the entire thickness of the epithelium and a complete loss of stratification. (×500.)

DR. RONALD R. GREENE, Chicago, Ill.—We have some data with almost identical results. Dr. Ben Peckham and I have been following patients with a diagnosis of basal-cell hyperactivity for four years. Our group division into degree of hyperplasia is a little different but that is not relevant. We have followed 142 patients during this period of time for at least six months and a maximum of four years. Approximately half of them have been followed twelve to twenty-four months. In 55 of 142, or 37 per cent, the epithelium has reverted completely to normal. In 75, or about half, the lesions have persisted with some minor variations in form. In 13, or 10 per cent, there has been a progress to preinvasive carcinoma of the cervix. I do not have these data broken down, but this was more common in those patients with more marked lesions when we first biopsied them. Our follow-up period is much too short to make definite statements. It is possible that a larger percentage of these lesions will eventually terminate in carcinoma but again, as Dr. Galvin said, almost half of them appear to regress and disappear spontaneously.

DR. GERALD A. GALVIN, Baltimore, Maryland (by invitation), (Closing).—In answer to Dr. Scott:

1. Were any of our cases associated with pregnancy? There was but one case in this entire series in which pregnancy was involved. In this case the cervical biopsy obtained at the time of completion of an abortion showed a marked degree of basal-cell hyperactivity. Further observation showed carcinoma in situ some two years later.

2. What was the mean age of this group as compared to our group of patients with carcinoma in situ? The mean age of this present group of patients was 43.4 years, while the mean age of approximately 200 patients with carcinoma in situ in our studies has been slightly more than 37 years.

3. Was there any associated vaginitis? I am unable to answer this question.

Dr. Scott wisely emphasizes the value of the cytological smear. In this study, I repeat, the smear was used extensively and proved of great assistance, particularly in indicating when to take a biopsy. At the present time, however, we are unwilling to adopt Dr. Scott's practice of relying almost exclusively upon the cytological picture and we still have far greater confidence in our histological interpretation of the biopsy.

Dr. Scott advances another point with which I take definite issue. He states that in 100 of his cases of carcinoma in situ the lesion was found in the portio in 10 of the cases, and in the canal in the remaining 90. He further implies that punch biopsy would have missed the 90 lesions in the canal. Now it is well known that carcinoma in situ rarely occurs independently in the portio and I am surprised that he finds the lesion here in as many as 10 per cent of his cases. The lesion practically always occurs at the squamocolumnar junction which is the target area for our punch biopsy. Occasionally, the lesion does occur far up in the canal but in our experience this is an uncommon finding; in this instance, however, we do miss the lesion with a punch biopsy and must rely upon the smear and cervical curettings.

Dr. Scott further criticizes us for assuming regression in 6 patients who were followed for relatively short periods. Perhaps we are presumptuous in making this statement. Of these 6 patients, however, while one had only three follow-up biopsies, two had four, one had five, and two had six. We feel that with repeated negative findings in follow-up biopsies, it is very likely that the original epithelial abnormalities in these cases did regress.

ETIOLOGY OF PRE-ECLAMPSIA-ECLAMPSIA

V. Extra- and Intracellular Fluid Changes and Electrolyte Balances*†

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OBSTETRICIANS have thought for many years that there was a direct relationship between the amount of clinical edema and the severity of the pre-eclampsia-eclampsia. In some cases they were puzzled, however, because they did not find this correlation; one patient might have marked edema with no hypertension or proteinuria, while another patient would have no edema but very marked hypertension, proteinuria, and the various symptoms associated with severe pre-eclampsia-eclampsia. Obstetricians have frequently noted that patients would gain rapidly without showing any demonstrable edema, and would lose this weight after delivery. Obviously, the marked changes in body weight must have been due in part to a retention of water and electrolytes somewhere in the body. Not infrequently the pre-eclamptic-eclamptic patient would show no edema at the first examintion by the doctor but two or three hours later there would be marked pitting over the tibia and particularly in the tissues of the face and yet the patient had not had any fluids during this period; again illustrating that there had been an abnormal accumulation of water and electrolytes somewhere in the body which had shifted within the period of a few hours and become clinically visible. These abnormal gains and losses in weight are demonstrable by periodic determinations of the patient's weight or of total body water, the latter a time-consuming procedure.

Much of the investigative work has been influenced by the signs noted late in patients with severe pre-eclampsia or eclampsia, namely, deep coma, anuria, hyperpyrexia, blood which either clots very rapidly or fails to clot; these signs were usually irreversible and the patients died. Since 99 per cent of the patients with pre-eclampsia and some 90 per cent of those with eclampsia recover, it is obvious that these patients had not reached the irreversible stage and that the edema, proteinuria, hypertension, convulsions, fever, tachycardia, hemoconcentration, etc., would respond to proper obstetrical treatment—meaning the correction of the abnormal physiology accomplished eventually by the removal of the pregnancy by the safest method.

We believe our weight determinations on a beam balance and intake and output studies with calculations of extra- and intracellular water, sodium, po-

*Supported in part by the Fiftieth Anniversary Fund for Eclampsia.

†Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

tassium, and chloride ions, as well as the nitrogen and phosphorus balances, indicate that in pre-eclampsia there are more than the usual changes of normal pregnancy. These changes become more marked in the patient with mild or compensated pre-eclampsia; but in the patient with severe or uncompensated pre-eclampsia the changes, especially in the amounts of intracellular water and electrolytes, are greatly altered, and it is the speed and degree of this disturbance in kidney, liver, brain, etc., which cause the various symptoms and signs. If the abnormal changes are too great, the condition becomes irreversible, and death occurs.

This is not an isolated report based on a few patients, but is part of a study in which specimens of rectus muscle and skin were analyzed for water, sodium, potassium, and nitrogen. Radioactive sodium was used for study of metabolism, sodium space, and exchangeable sodium. Radioactive serum albumin is used for plasma volume and protein clearance. Deuterium oxide is being used for total body water. Biopsies of the liver and kidney have been obtained to aid in the diagnoses. During the course of the studies, various solutions, such as dextrose, saline, sodium lactate, sodium bicarbonate, potassium chloride, gum acacia, serum albumin, and plasma, as well as many hormones and drugs, have been administered to the patients with the idea either of improving the clinical condition or of altering it by some measurable agent, such as test loads of hypertonic sodium chloride solution, DOCA, cortisone, etc. The usual clinical determinations of blood pressure, 24 hour proteinuria, urea clearance, Addis count, retinal examination by an ophthalmologist, etc., were made.

Many of the patients were studied in previous or subsequent pregnancies, which enabled us[11] to correct any faulty diagnosis. In some patients we have as many as five pregnancies and two or three renal biopsies, all separated by one or more years. Our studies have always been to determine what physiological changes occurred in the patient with pre-eclampsia or eclampsia during the disease and during the puerperium which might yield knowledge of the original condition.

During the past twenty-five years we have seen a pattern of water and electrolyte imbalances become apparent in patients with pre-eclampsia-eclampsia which accounts for the various signs and symptoms of severe true pre-eclampsia or eclampsia without the need for any toxins. Factors which still have to be considered are the reasons for the increased incidence of pre-eclampsia in primigravidas, multiple pregnancy, polyhydramnios, and hydatidiform mole. The first three all have a common factor of increased intrauterine, intra-abdominal, and inferior vena cava pressure; the latter two will decrease urine secretion even to anuria and cause decreased hepatic function. The pre-eclampsia and occasional eclampsia associated with hydatidiform mole may be similar in etiology, i.e., rapid distention of the uterus, or it may be a different clinical condition.

Some seventy-five years ago, eclampsia was ascribed to water intoxication. Some thirty years ago it was thought to be due to an excess of salt. Various toxins from placenta, food, etc., have been considered the cause by some observers.

During the past twenty-five years pre-eclampsia-eclampsia has been attributed to an excess of the sodium ion. The signs and symptoms associated with pre-eclampsia and the convulsions and coma with eclampsia are not peculiar to these conditions. The hypertension, edema, proteinuria, convulsions, coma, hyperpyrexia, etc., have been reported in nonpregnant females and in males, being caused by the excessive ingestion or administration of water and/or electrolytes in normal patients and animals. The same symptoms and signs will occur in patients with prolonged oliguria or anuria due to incompatible blood transfusions, carbon tetrachloride poisoning, cortical necrosis of the kidney, etc., who were given normal amounts of water and electrolytes.

Previously reported studies [3, 4, 5] show that the normal pregnant patient has a delayed elimination of water and of the sodium ion (the latter being due to a decreased ability of the kidney to concentrate the sodium ion and the decreased urinary output), an increased pressure in the inferior vena cava, an increased permeability of the capillaries, a hemodilution, etc.; all are intensified in pre-eclampsia. A patient with pre-eclampsia, until it becomes severe, will have a hemodilution which may be even greater than the normal for the period of pregnancy, but when the condition becomes severe, she will have a relative (for pregnancy) or absolute concentration of the blood. [5, 6, 7] Thus fluid will diffuse from the vascular system into the already abnormally enlarged interstitial space. Schwarz and Dieckmann [26] in 1929 reported their observations on hemoconcentration in severe pre-eclampsia and eclampsia, and also stated that there was some correlation between the marked excretion of chloride during the puerperium and the weight loss of the patient.

Dieckmann[7] in 1936 reported changes in blood and plasma volume in pre-eclampsia-eclampsia, stating that the decreased blood volume was not the cause of eclampsia but it was intimately associated with the convulsions, coma, oliguria, and the other symptoms characteristic of the disease, and that an increase in plasma volume preceded clinical improvement. If it did not occur, the patient died. We pointed out the seriousness of hemoconcentration and mentioned the paradox of the water-logged individual, in whom fluid would leave the vascular system to go into the already enlarged interstitial fluids. Dieckmann[8, 9] stated that the edema was not due to a hypoproteinemia, but was caused by the increased venous pressure in the legs, the increased capillary permeability, and the decreased elimination of water and sodium by the kidney. In 1941 we[9] reported sodium, chloride, and potassium balances in pre-eclamptic patients and in 1952 we[6] reported, so far as we know, the first calculation of extra- and intracellular water and electrolytes in a pre-eclamptic patient. We have stated repeatedly that if one can produce a permanent hemodilution by hypertonic dextrose solution, serum albumin, dextran, or other treatment, the patient clinically improves.

We[10] have reported that the pregnant patient who is normal, or who has pseudo-pre-eclampsia or benign hypertensive disease will tolerate two or more daily intravenous injections of 1,000 ml. of a 2.5 per cent NaCl solution without any increase in hypertension, proteinuria, or the development of symptoms. The patient with pre-eclampsia has a marked rise in blood pressure, a tremendous increase in the proteinuria, and usually develops the typical symptoms.

In 1946 we acquired a beam balance sensitive to 0.2 gram for weighing patients. A climate room in which constant temperature and humidity can be maintained was completed in 1947. We learned that the beam balance and climate room were not enough. The door to the lavatory opening off the climate room had to be locked and the key kept by the nurse in charge. Two assistant nurse supervisors and a dietitian have a portion of their salary paid from research funds for special care of the patients in the metabolic room. A minimum of two, and for some years four, chemists gave full time and one resident gave much of his time. We have listed the personnel and some of the difficulties to indicate that we have made as careful a study as feasible. Many of the studies were not completely usable because patients would go into labor or the pregnancy had to be terminated to save the mother and/or baby's life. We did not correct or interpolate for missing data; the case was not used. Normal pregnant patients were unwilling to stay in the hospital, eat the same diet daily, collect urine, have numerous venipunctures, and be generally uncomfortable. However, we have sufficient data from some cooperative normal patients, and the patients with mild hypertensive disease also serve as controls.

All of us unconsciously know that the normal body is most adept in adjusting to and excreting the large amounts of water, electrolyte, and food which the average individual consumes. We are conscious of feelings of fullness and tightness in the abdomen after a large meal or large amounts of liquids. Some of us have symptoms in other portions of the body but, in time, there is a complete adjustment although the weight will still be increased. The possibility is always present of a failure of this balancing power which happens if one of the excretory organs becomes temporarily or permanently impaired and the balance then becomes abnormal. There is irrefutable evidence which indicates that the extra- and intracellular compartments of the body are in equilibrium and that the plasma is in equilibrium with the interstitial fluid. Normally, there is no "iron curtain" between the three compartments; however, there is a "veil" in pre-eclampsia, and a thinner "veil" in normal pregnancy.

We are certain of the changes in weights and of the electrolyte balances. We have not corrected for the fecal loss of the various substances studied or for the loss in sweat. Patients are kept in a constant temperature and humidity room during the study. In eight patients the average daily fecal losses were 0.4 meq. Na; 3.0 meq. K; and 1.0 meq. Cl. We have also extracted the pajama pants and coat (and found 5 meq. Na; 1.5 meq. K; and 7 meq. Cl) as well as washed the patient in the morning with distilled water to determine the loss of sodium and chloride (1-2 meq. Na; 1-4 meq. Cl; and 1 meq. of K).

The insensible loss in a few patients in the climate room (80° F., relative humidity 50 per cent) ranged from 1,800 to 2,600 Gm. of water per 24 hours. All of these values are insignificant when compared with the positive or negative balance values we are discussing (changes of 200 to 1,100 meq. Na).

The formulas used for calculating extra- and intracellular fluid and electrolyte concentration were reported by Elkinton and associates.[12] Those used for the total extra- and intracellular Na, K, Cl calculations are based on Deane and Smith's[2] study. The various amounts of fluid or electrolyte are not exact but they do show a consistent pattern for pre-eclampsia-eclampsia.

TABLE I. COMPARISON OF UNCORRECTED CALCULATIONS WITH CORRECTED FOR WATER OF SERUM AND DONNAN FACTOR. CASE 2.

		EXTRACELLULAR FLUID					INTRACELLULAR FLUID					
		TOTAL		CHANGE IN			TOTAL			CHANGE IN		
CALCULATIONS	DATE	E. C. F. (L.)	Na (MEQ.)	E (L.)	Na (MEQ.)	K (MEQ.)	I. C. E. (L.)	Na (MEQ.)	K (MEQ.)	I (L.)	K (MEQ.)	DISCREPANCY OF BASE* (MEQ.)
Corrected	8/24	24.2	3,257.7	−0.4	+21.3	+4.0	34.1	954	3,328	−1.1	−7.8	+20.8
Uncorrected	8/24	25.7	3,394.5	−0.4	+26.9	+4.3	32.6	774	3,362	−1.1	−8.1	+22.4
Corrected	9/1	13.4	1,839.8	−0.6	−69.2	−4.3	31.7	1,226	3,293	+0.1	−26.2	−112.3
Uncorrected	9/1	13.5	1,813.0	−0.7	−79.6	−6.4	31.6	1,208	3,234	+0.2	−24.1	−112.9

*Discrepancy or osmotically inactive base.

All calculations were made without correcting for the water content of the serum or the Donnan effect. The water was determined in some sera and could have been calculated in all determinations from the serum protein concentration and is approximately 93 per cent. In Table I we have given the values for the beginning and end of the metabolic period with the corrections and uncorrected. It is obvious that, although there is a difference, it is comparatively small and does not warrant the additional work of correcting.

We have determinations of total body water with antipyrene and of extracellular fluid volume with thiocyanate, a few with inulin, and some with Na^{22}. The antipyrene and thiocyanate values are inconsistent, possibly due to too slow diffusion in the pre-eclamptic patient. Thus we find extra-cellular fluid volume comprising a greater per cent of the body weight post partum than ante partum when edema was still present. Furthermore, the per cent of body weight for extracellular fluid is too high when compared with intracellular. Thus Case 1 had an antepartum total body water of 55 per cent and extracellular of 39 per cent, while comparable postpartum figures were 43 and 33 per cent. All of our calculations begin with the last metabolic day in the puerperium, when we thought the patient was normal, but we now know that, even at ten days, the extra- and intracellular compartments are still abnormal. We assumed on this last day that 20 per cent of the body weight was extracellular fluid, and that 70 per cent of the body weight was water. The latter value is now known to be too high. The changes in the extra- and intracellular water and electrolyte may be greater or less than our calculations show, but the direction of change is the same.

Results

The various concentrations of electrolytes in the plasma and by inference in the interstitial and intracellular fluids are controlled within narrow limits in the normal subject. The interstitial fluid contains 150 meq. of base, of which almost all is sodium (3.2 Gm. of sodium) (8.2 Gm. of sodium chloride). One kilogram of interstitial fluid contains that amount of base or sodium chloride or that amount of base can attract or hold 1 kg. of water. In Fig. 1, we have graphed the changes in beam-balance weight against the sodium balance. Theoretically, if the patient lost a kilogram of weight in twenty-four hours, there should be a loss of 150 meq. of sodium, or a similar retention, if she gained a kilogram. The data represented by the open circles in the lower right quadrant were all obtained after delivery, and the solid circles before delivery. If there had been an isotonic retention of water and sodium, the dots would fall along the line bisecting the right angle. Since the majority of the dots lie above this line, it indicates that more water is excreted than sodium, suggesting (1) that the extracellular fluid was hypotonic, or (2) that some of the water was intracellular in origin where it was possibly in association with a potassium salt. These findings indicate that there must have been a marked disturbance in the body physiology. The urinary chloride and sodium concentrations tend to be equimolar.

The solid triangles in the upper left quadrant represent similar changes occurring before delivery in various types of pregnant patients who were given 1,000 ml. of a 2.5 per cent solution of sodium chloride intravenously. These balances are calculated on a twenty-four hour basis, but in some patients, who received daily injections, the findings are essentially the same, namely, that more sodium was retained than water. In other words, had there not been some re-

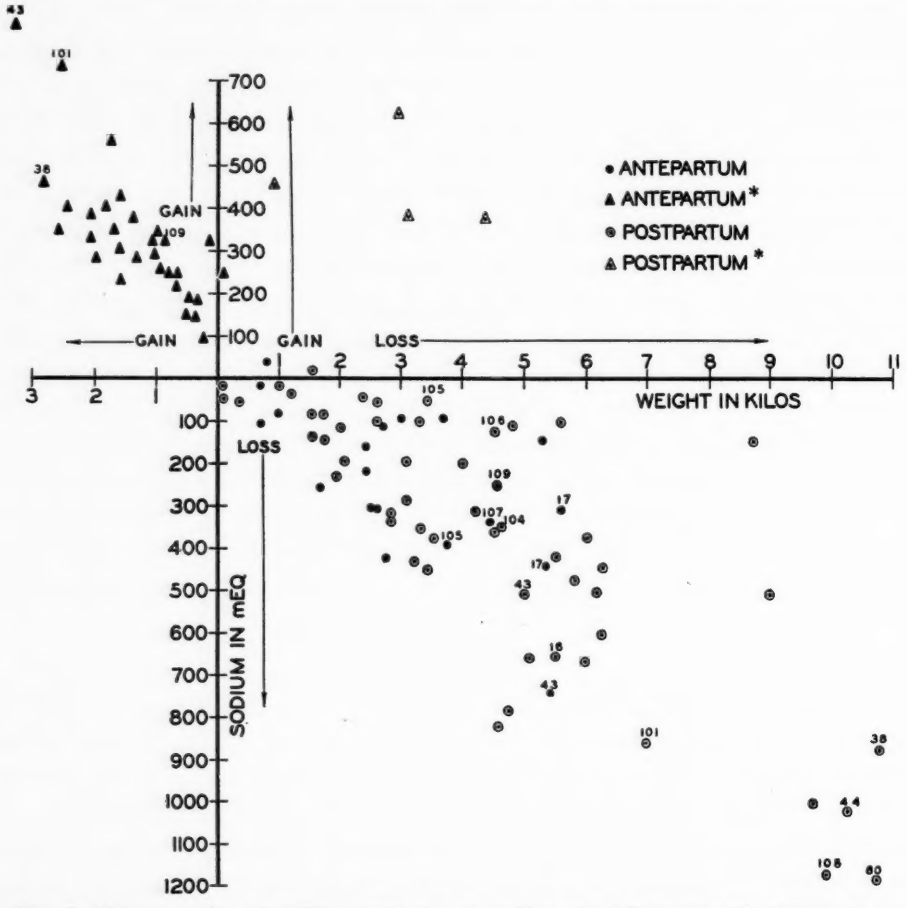

Fig. 1.—Shows ratio of milliequivalents of sodium to kilograms of change in weight. The solid circles represent ratios on antepartum and the open circles on postpartum losses. Since most of the dots are above a line bisecting the angle, more water than sodium was lost. The solid triangles are ratios of 24 hour balances after an intravenous injection of 1,000 ml. of 2.5 per cent NaCl solution and indicate more than 150 meq. of Na per kilogram gain.

adjustment between the body compartments, the extracellular fluid would have been hypertonic, as the plasma is during the injection. Either the sodium was stored where its osmotic properties were reduced, namely, in the cells, or the interstitial fluids were hypertonic for a period of time, which is incompatible with the normal body physiology.

The few open triangles represent losses in weight but gains in sodium, two indicate an excess of sodium and one a lack.

The data in Table II show the average milliequivalent of base per kilogram of change in weight. In general, there was more base per kilogram excreted

post partum; this is especially evident in the pre-eclamptic patients. Similarly, all postpartum patients after the hypertonic saline solution showed a much lower ratio for milliequivalents of sodium per kilogram, because of the greater excretion of the sodium after delivery.

TABLE II. MILLIEQUIVALENTS OF SODIUM AND CHLORIDE PER KILOGRAM OF WEIGHT CHANGE

	LOW Na AND K DIET				TEST LOAD OF NaCl			
	ANTE PARTUM		POST PARTUM		ANTE PARTUM		POST PARTUM	
DIAGNOSIS	Na	Cl	Na	Cl	Na	Cl	Na	Cl
Normal pregnant	50	30	85	105	347	343	173	161
Hypertensive disease	72	66	79	93	213	233	189	172
Chronic glomerular nephritis	44	27	42	65	308	277		
Pre-eclampsia-eclampsia	87	75	101	104	264	253	178	141

The pregnant patients who were normal, or who had hypertensive disease, or chronic glomerulonephritis were able to handle the test load of sodium chloride solution even when given as much as 325 Gm. (5,600 meq.) of sodium chloride intravenously in twelve days, and some patients received as much as 42 Gm. (725 meq.) of sodium chloride intravenously and by mouth daily.

We have over 24 patients with benign hypertensive disease or chronic nephritis who were given daily intravenous injections of 1,000 ml. of a 2.5 per cent sodium chloride solution (maximum 12 injections) and had positive Na balances ranging from 204 to 1,000 meq. but all either *lost* 1 to 6.7 kilograms or the weight was unchanged; none gained, although the sodium retention should have caused an *increase* of weight of from 1 to 7 kilograms. Where these sodium ions are retained, in bone, in extra- or intracellular compartments or both, is an important question.

We found that the average-sized patient with hypertensive disease gained during pregnancy and lost in the puerperium about the same as the normal pregnant patient. The obese pregnant patient with hypertension had somewhat greater gains in pregnancy and losses in the puerperium. The pre-eclamptic patient had a marked gain in pregnancy and loss in the puerperium. It must be kept in mind that most of the pregnancies in these patients with pre-eclampsia-eclampsia were terminated before term. The weight gain, had the pregnancy gone to term, would have been much more, with resultant greater changes in the volume and composition of the body compartments. For many years we have been more concerned with the patient who shows rapid and marked increases in a period of several weeks than in the patient who has a constant excessive gain. The patient who gains 3 to 10 kilograms in a period of four to six weeks is much more likely to develop pre-eclampsia than the patient who gains 10 to 20 kilograms in the entire duration of pregnancy.

Table III lists pertinent data for selected patients, for some of whom there are also graphs. Serum Na and Cl were abnormally low only in Case 3 (M. H.) who had an ileus with vomiting. None were abnormally high. Serum K was within normal range. Na and Cl showed changes in concentration of as much as 6 meq. but remained in the normal range; however, such changes would cause considerable alterations in extra- and intracellular fluids.

TABLE III. EXTRA- AND INTRACELLULAR CHANGES, BALANCES, AND SERUM SODIUM AND POTASSIUM CONCENTRATIONS

CASE	NO.	DIAGNOSIS	DAYS	MEANS: SERUM CONCENTRATION (MEQ.)		BALANCE—MEQ. TOTAL PERIOD				TOTAL BODY		CHANGE IN EXTRACELLULAR			CHANGE IN INTRACELLULAR			DISCREPANCY OF BASE† (MEQ.)
				Na	Cl	Cl	Na	K	N (GM.)	WEIGHT (KG.)	H_2O (L.)	H_2O (L.)	Na (MEQ.)	K	(H_2O) (L.)	Na (MEQ.)	K	
R. I.	108	Pre-eclampsia	3 A. P.	133	106	− 95	− 52	− 34	+ 2	− 2.5	− 2.9	− 2.0	− 327	− 3	−1.0	+275	− 31	− 462
			5 P. P.	132	105	−1221	−1106	−136	−43	− 9.3	−10.3	−10.5	−1321	−57	+0.2	+215	− 79	− 23
M. S.	101	Pre-eclampsia*	6 A. P.	133	99	+ 779	+ 891	+ 72	−12	+ 2.7	+ 2.7	+ 7.1	+1023	+35	−4.4	−132	+ 36	− 588
			10 P. P.	136	99	− 581	− 787	+ 70	+ 1	− 7.3	− 7.3	− 6.4	−1032	−33	−0.9	+245	+102	− 821
H. J.	16	Pre-eclampsia*	3 A. P.	142	101	− 180	− 184	− 72	− 5	− 1.6	− 1.6	− 1.9	− 464	−11	−0.3	+280	− 61	− 98
			5 P. P.	132	102	− 497	− 392	−123	−18	− 4.4	− 4.4	− 3.6	− 501	−21	−0.8	+109	−103	− 68
M. L.	42	Pre-eclampsia	5 A. P.	135	107	+ 104	− 482	−154	+ 7	− 5.3	− 5.3	+ 0.4	− 103	− 9	−5.7	−379	−145	− 691
			7 P. P.	128	96	− 332	+ 30	− 1	− 5	− 1.3	− 1.3	− 1.4	− 211	− 4	+0.1	+241	+ 3	− 320
E. L.	103	Pre-eclampsia*	10 A. P.	134	107	− 0	+ 46	−161	+ 3	− 4.6	− 6.6	− 0.2	+ 101	−10	−6.4	− 55	−151	− 468
			5 P. P.	134	106	− 223	− 76	− 72	−20	− 2.9	− 1.8	− 1.1	− 169	− 5	−0.7	+ 93	− 67	− 229
B. C.	106	Pre-eclampsia	7 A. P.	135	108	− 197	− 322	+ 13	− 1	− 4.4	− 5.3	− 1.6	− 333	−15	−3.7	+ 11	+ 28	− 779
			9 P. P.	133	101	− 161	− 171	+ 5	−11	− 4.0	− 4.1	− 3.6	− 373	−24	−0.4	+202	+ 29	− 168
G. L.	43	Pre-eclampsia	8 A. P.	138	109	+ 822	+1001	−100		+ 6.2	+ 6.2	+ 8.7	+1287	+11	−2.5	−286	−111	− 177
			6 A. P.	142	111	− 71	− 736	− 74		− 5.1	− 5.1	− 1.8	− 127	+ 4	−3.3	−609	− 78	+ 534
M. H.	38	Eclampsia	8 A. P.	113	97	+ 342	+ 449	− 59	+ 2	− 1.5	− 1.5	+ 3.1	+ 210	− 0	−4.6	+239	− 58	−1112
			10 P. P.	119	100	− 528	− 869	+ 79	+ 2	−10.9	−10.9	− 4.6	− 635	−22	−5.7	−234	+101	− 299
B. K.	109	Hypertensive disease*	6 A. P.	137	102	+ 279	+ 346	− 80	−10	+ 1.4	+ 1.4	+ 2.0	+ 215	− 7	−0.6	+131	− 87	− 297
			3 P. P.	137	100	− 188	− 157	+ 21	− 3	− 4.5	− 4.5	− 1.9	− 258	−10	−2.6	+101	+ 31	− 519
R. K.	114	Hypertensive disease	7 A. P.	132	101	− 402	− 251	− 69	−25	− 1.6	− 2.9	− 2.7	− 506	−12	−0.3	+257	− 35	− 501
			8 P. P.	133	96	− 449	− 65	− 68	−21	− 3.7	− 4.5	− 5.3	− 674	−41	+0.9	+608	− 28	− 309
J. C.	111	Hypertensive disease	11 A. P.	137	104	− 861	− 511	+ 92		− 5.9	− 5.9	− 7.6	−1142	−21	+1.7	+632	+ 83	− 191
			6 P. P.	136	100	− 734	− 800	− 71		− 4.7	− 4.7	− 7.3	− 889	−47	+2.6	+ 89	− 24	+ 409
D. B.	30	Hypertensive disease	12 A. P.	135	106	+ 83	+ 117	−111		− 5.9	− 5.9	+ 0.8	+ 105	+ 4	−6.7	+ 12	−115	− 587
G. C.	60	Hypertensive disease*	3 A. P.	134	99	− 205	− 304	− 37	−27	− 2.5	− 2.5	− 2.1	− 213	− 5	−0.4	+ 91	− 33	+ 151
			10 P. P.	136	99	+ 541	+ 478	+ 5	+10	− 2.8	− 2.9	+ 5.2	+ 719	+16	−8.1	−241	− 11	− 738
I. W.	52	Hypertensive disease*	7 P. P.	139	103	+ 375	+ 457	− 56	−24	− 1.4	− 1.4	+ 4.3	+ 488	+22	−5.7	− 31	− 78	− 543
L. G.	107	Normal (obese)	7 A. P.	134	102	− 243	− 358	− 86	−10	− 4.7	− 5.9	− 2.8	− 430	−23	−2.3	+ 72	− 63	− 483
			4 P. P.	134	104	− 10	+ 17	− 16	−22	− 1.6	− 2.3	+ 0.1	+ 8	+ 0	−2.3	+ 8	− 16	− 327
B. E.	112	Normal	6 A. P.	138	102	+ 87	+ 300	− 23		− 1.8	− 1.8	+ 1.0	+ 116	+ 6	−2.8	+178	− 12	− 654
			6 P. P.	134	99	− 37	+ 172	− 42		− 2.0	− 2.0	− 0.4	− 50	− 2	−1.6	+222	− 40	− 16

*This means that the patients had one or more intravenous injections of hypertonic NaCl solution.

†Discrepancy or osmotically inactive base, in calculations of total base.

There is a parallelism between the magnitude of losses or gains in weight and the magnitude of positive or negative Na and Cl balance. Most of the K balances were negative after delivery but there is no apparent constant relationship to the degree of change in weight, Na, or Cl.

Nitrogen balances (N. P. N., i.e., protein, was precipitated before analysis) were negative in large amounts in pre-eclamptic and eclamptic patients. A retention of urea would account for only a small portion. We have no other explanation except that their metabolism is increased. Phosphorus was usually either positive or negative but in small amounts and we considered the patient in balance. The direction of change in weight and water are always the same but the amount is occasionally different.

There is a considerable decrease in extracellular water, sodium, and chloride after delivery with small decreases in potassium. Intracellular water showed decreases ranging from 1 to 8 L.; sodium in relatively large amounts moved into the cells.

A column labeled "discrepancy of base" is a moot point of discussion. Elkinton,[12, 28] Iseri,[19] and other[23] investigators have noted that after all possible errors have been accounted for, there is a difference, usually of considerable magnitude, between the calculated and determined total base and balance for the total body water. It is postulated that a portion of base does not attract its share of water because it is probably intracellular. The positive signs indicate that that amount of base was activated during the period and the negative indicate that the base was osmotically inactive.

It is difficult to accept such a concept except that, when we inject intravenously large amounts of hypertonic NaCl solution, there is not a proportional increase in weight for the period of study, and either the extracellular fluid is permanently hypertonic, which studies show does not occur, or some Na has become intracellular. Eventually this excess base is eliminated, but in pre-eclamptic patients this may require three to six days, yet the serum Na and Cl have returned to their preinjection values in a few hours.

Case 1 was an 18-year-old Negro primigravida who was at term on Sept. 1, 1954. She was treated at one of the city clinics and her pregnancy was presumably normal until August 13, when she had a 4 plus proteinuria, a blood pressure of 130/80, and no recorded edema, although in a period of four months she had gained 17 kilograms. Clinical data are given in Table IV. There was marked edema of the legs and of the abdominal wall. A retinal examination showed a hypertensive retinopathy. There was a twin pregnancy. The patient was treated with a low sodium and potassium diet and 250 mg. of Diamox daily, as well as digitalis because of the fear of pulmonary edema. She lost 3.5 kilograms before delivery. The products of conception weighed 7.9 kilograms and during the first 9 days of the puerperium she lost an additional 11.3 kilograms. The marked loss of water, electrolytes, and nonprotein nitrogen is depicted in Fig. 2. Note the small negative balance of Na and Cl until delivery, when a tremendous loss began. There was a total loss of 1,139 meq. of sodium, 1,274 meq. of chloride, 164 meq. of potassium, 49 Gm. of nitrogen, and 2.8 Gm. of phosphorus in six days.

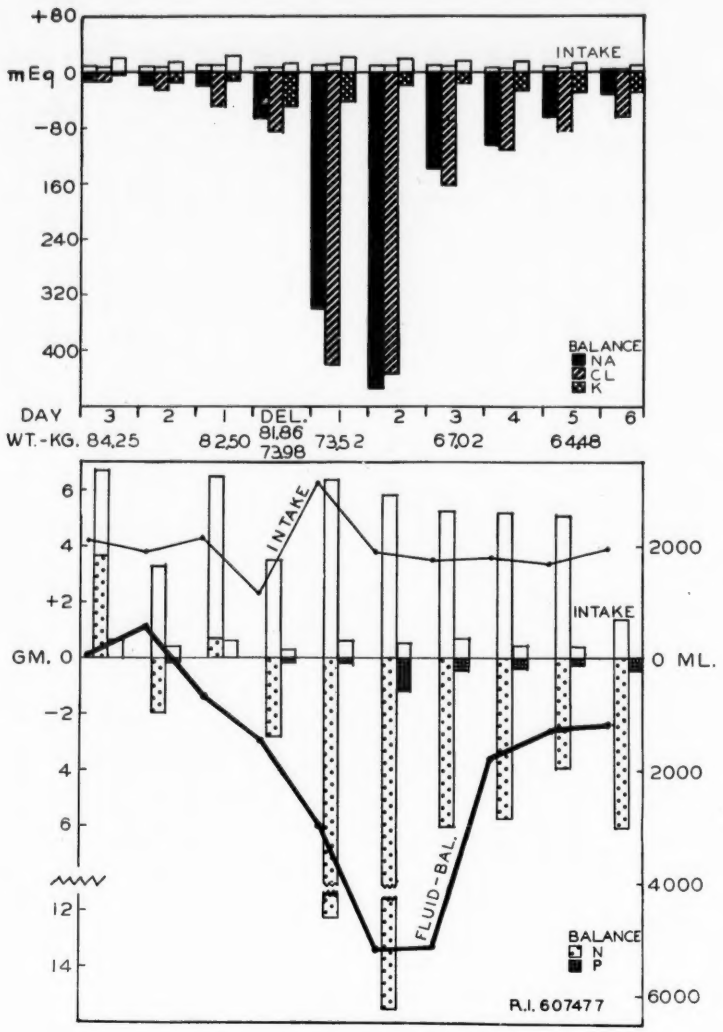

Fig. 2.

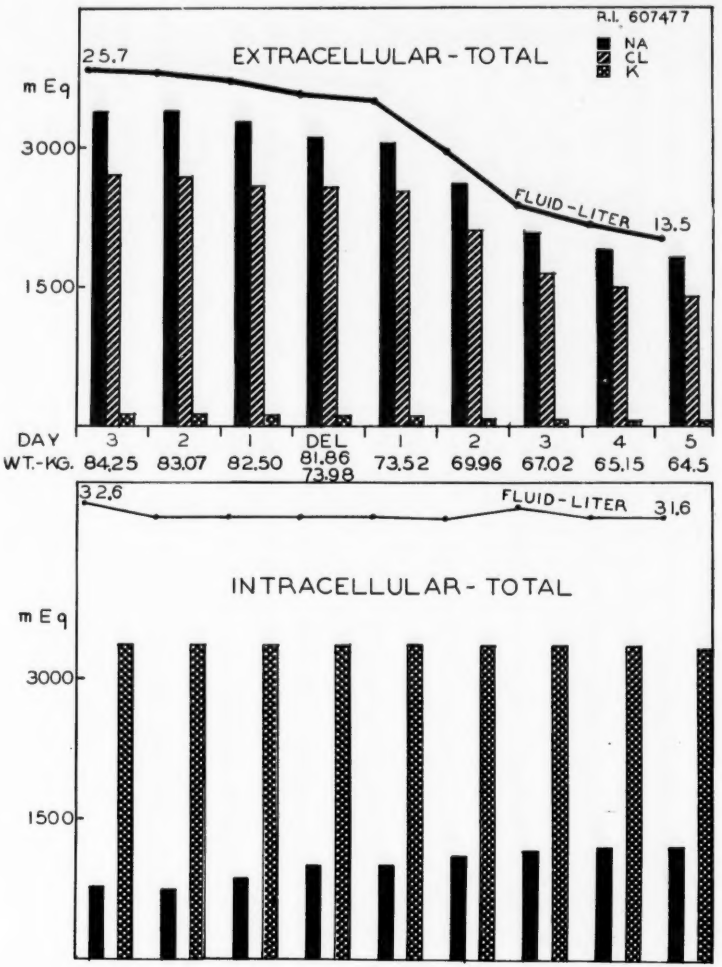

Fig. 3.

Fig. 2.—Case 1. (R. I. No. 108) Pre-eclampsia. Balance shows comparatively little antepartum loss of Na, Cl, and N, as compared with the tremendous negative balances which indicate the marked retentions which had been present before delivery.

Fig. 3.—Case 1. Total fluids show decrease of 12.2 L. from the extracellular compartment with a large loss of Na and Cl, while the intracellular fluid gained Na.

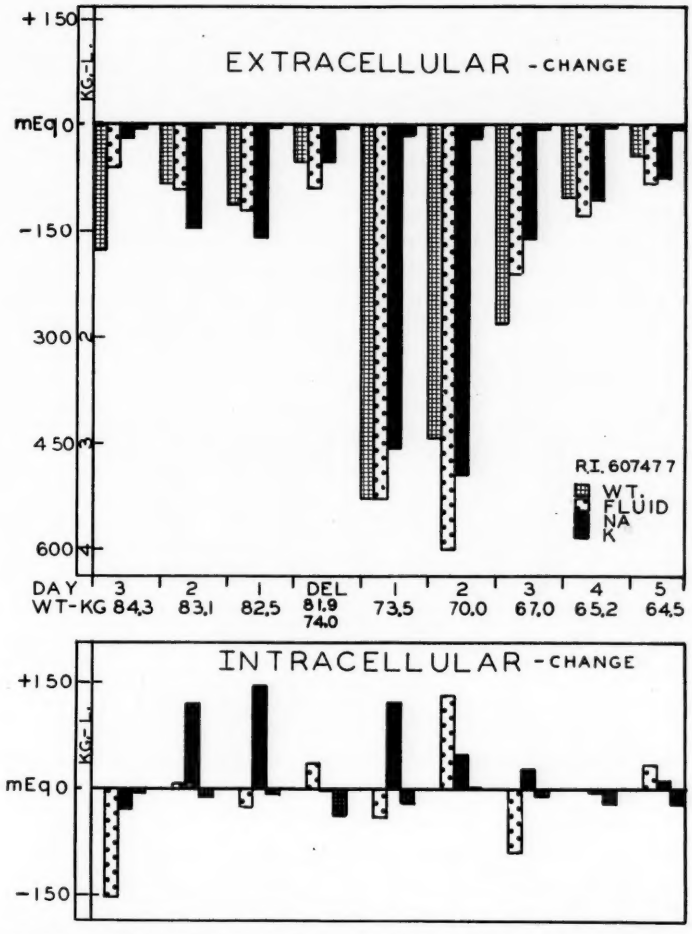

Fig. 4.—Case 1. Daily changes show antepartum shift of Na from extra- to intracellular fluid; post partum there are tremendous losses of water, Na, and Cl from the extracellular compartment with increases of intracellular Na.

TABLE IV. CASE 1. SEVERE PRE-ECLAMPSIA, LOW SODIUM AND POTASSIUM DIET

1954 DAY	WEIGHT (KG.)	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	HEMATOCRIT (%)	SERUM PROTEIN (GM. %)	SERUM (MEQ.) Cl	Na	K
4 Admission	85.17	++++	160/100	5.5	32	4.8	106	134	5.2
3	84.25	+++	170/95	5.6	30	4.6	105	132	4.9
2	83.07	+++	140/80	5.4	32	5.3	106	135	5.1
1	82.5	+++	145/80	3.7					
Delivery A. P.	81.75	+++	175/95	5.5	30	4.8	109	130	5.1
P. P.	73.98	++	160/95						
1	73.52	++	145/85	4.2					
2	69.96	++	145/95	1.8					
3	67.02	+	160/100	1.5	30	4.6	105	132	4.9
6	64.20	0	120/70	1.1	34	5.3	101	135	4.8
9 Discharge	62.70	0	115/70	1.1					
		Extracellular fluid				1.84	114	135	4.8
		Amniotic fluid—Baby I					111	128	6.0
		Amniotic fluid—Baby II					109	127	5.6
		Muscle, gastrocnemius, fat free, wet						49	94.0
		Skin						102	21.3

DAY	VOLUME (L.) TOTAL WATER	EXTRACELLULAR	BLOOD	SERUM	LEG
4 ante	47.0	33.0	5.33	3.85	33.9
7 post	26.8	20.8	3.78	2.56	24.0

TABLE V. CASE 2. ECLAMPSIA, LOW SODIUM AND POTASSIUM DIET

1953 DAY	WEIGHT (KG.)	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	HEMATOCRIT (%)	SERUM PROTEIN (GM. %)	SERUM (MEQ.)			VOLUME (L.)	
							Cl	Na	K	BLOOD	SERUM
33	61.4		110/70	0							
12	65.8	+	130/90	0							
1 Admission		++	210/155	15.0							
Delivery A. P.		++	190/120		49.0	6.2	106	138	5.4	4.85	2.72
P. P.	65.32	++	205/150		46.0	6.1	106	141	5.6		
1	65.88	+	140/110	2.3	30	4.3	106	137	5.6		
2	63.84	+	150/100	2.0							
3	61.5	0	130/80	3.7							
5	58.2		150/85	4.4							
8	54.59		135/85		35	6.2	100	138	5.2	3.70	2.38
10 Discharge	53.5	0	130/80	3.2							
22	53.3		110/75	1.0	44	7.9					
59	54.6		105/80	0.1							

ADDIS COUNT	PROT. (GM.)	CASTS	RBC	WBC	EPITH.
		MILLIONS			
Admission	15.0	48	122	6	18
Discharge	3.2	0	94	2	1

Fig. 3 shows that most of the weight loss was from the extracellular fluid; there were marked decreases in sodium and chloride and were considerable increases of intracellular sodium.

Fig. 4 shows a decrease in extracellular fluid of 12.2 L., of 1,581 meq. of sodium, of 1,320 meq. of chloride, and approximately a 50 per cent decrease in extracellular potassium. There was a decrease of approximately 1 L. of intracellular fluid, an increase of 434 meq. of intracellular sodium. In this patient the primary retention had been in extracellular fluid, but the intracellular fluid had been affected by a marked decrease in sodium which was replaced as the patient showed clinical improvement.

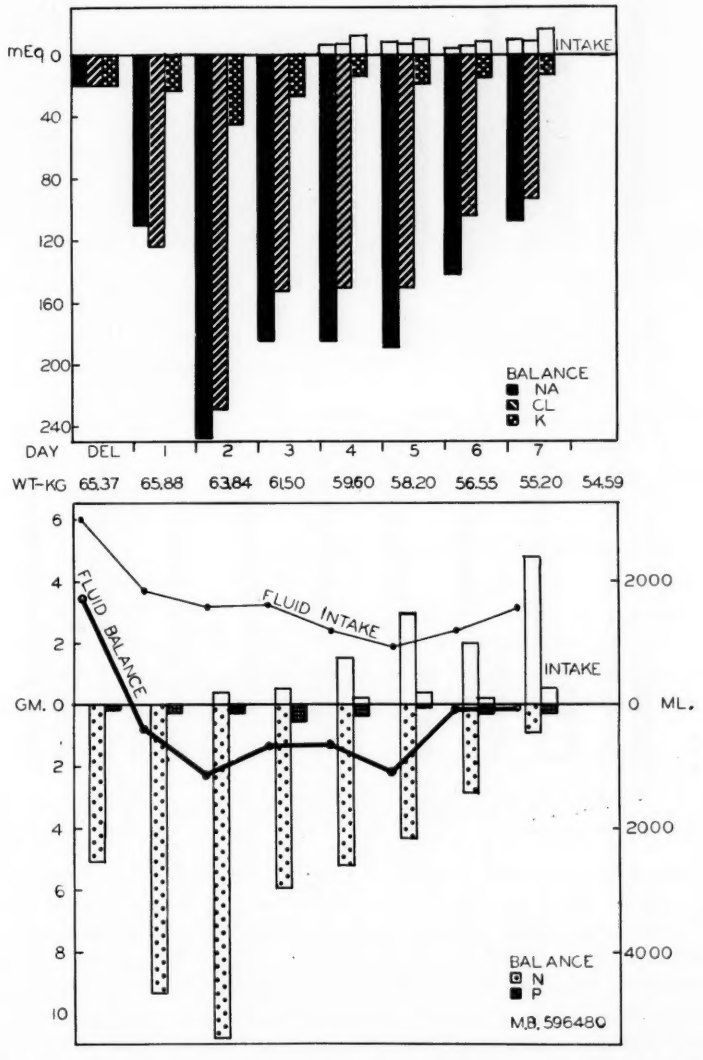

Fig. 5.—Case 2. (M. B. No. 80) Eclampsia. Balance studies show marked loss of Na, Cl, K, N, P, and water as weight decreased. Kidneys had normal function shortly after delivery.

The serum electrolytes were within the normal range and interstitial fluid obtained from the leg had essentially the same values as the plasma water as shown in Table IV. The gastrocnemius muscle contained a normal amount of

sodium. The concentrations of sodium, potassium, and chloride in both amniotic fluid cavities were essentially the same. Antipyrine gave a total body water of 47 L. on admission and 26.8 L. on discharge. The extracellular thiocyanate fluid determination decreased from 33 L. to 20.8 L. but the extracellular fluid presumably rose from 70 to 78 per cent of the total body water, indicating faulty diffusion of the thiocyanate and antipyrene.

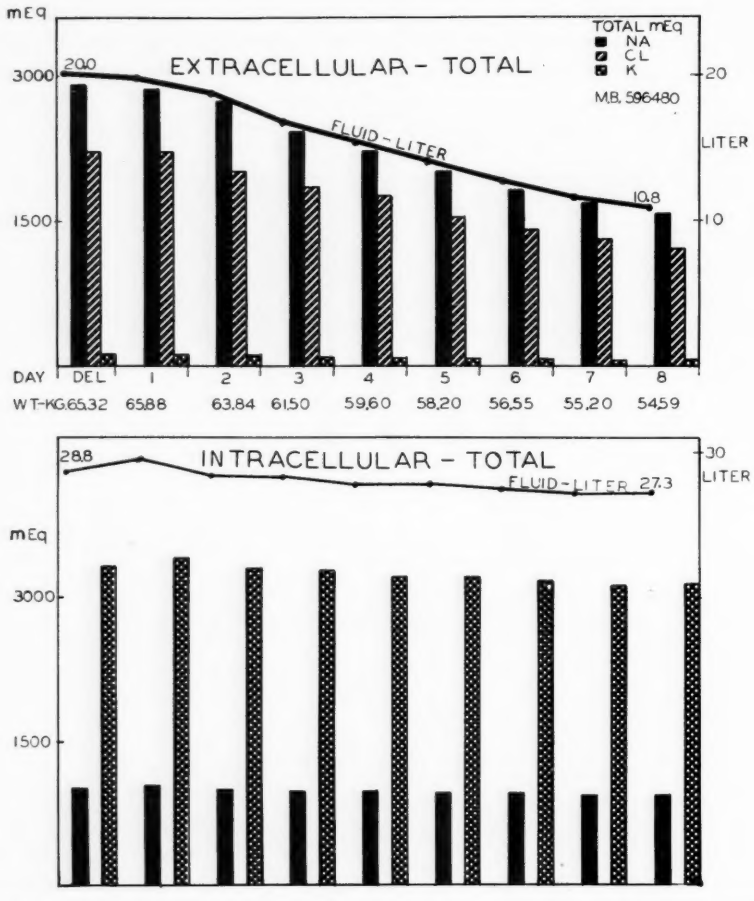

Fig. 6.—Case 2. Total fluids show marked decrease in water, Na, and Cl in extracellular and almost unchanged intracellular compartment.

Case 2 was a 16-year-old Negro primigravida who came from one of the city clinics. She was at term on April 11, 1954 and was admitted on March 10, 1954, having had two convulsions which were followed by two more after admission. The blood pressure was 210/115, proteinuria 4 plus and edema 2 plus. Sedatives and intravenous injections of 1,000 ml. of 20 per cent dextrose solution were given. The patient was in labor, and delivery was hastened by amniotomy. She delivered a 1620 gram fetus that survived. The first accurate weight determination was immediately after delivery and in the next eight days she lost almost 11 kilograms. Table V shows blood, urine, and some clinical findings. The patient received only parenteral fluids for 48 hours and then an increasing low sodium and potassium diet. Thus, for almost 96 hours, the intake of electrolyte was minimal. Fig. 5 shows negative balances amounting to 1,118 meq. of Na, 178 meq. of K, 1,018 meq. of Cl, 44.0 Gm. of N, and 1.75 Gm. of P.

Fig. 6 shows the calculated total changes in extra- and intracellular fluids and electrolytes. For a 9 L. decrease in extracellular fluid there is an almost 1,329 meq. decrease in sodium, and 1,011 decrease in chloride. The extracellular potassium decreases almost 50 per cent. The intracellular fluid volume decreased only 1.5 L. and the intracellular sodium and potassium remained almost constant. The changes may be less or more, as explained earlier.

Fig. 7 shows consistent marked losses primarily in the extracellular fluid after the first day. Water and sodium decreases were proportional. The intracellular fluid loses water and potassium, but gains sodium.

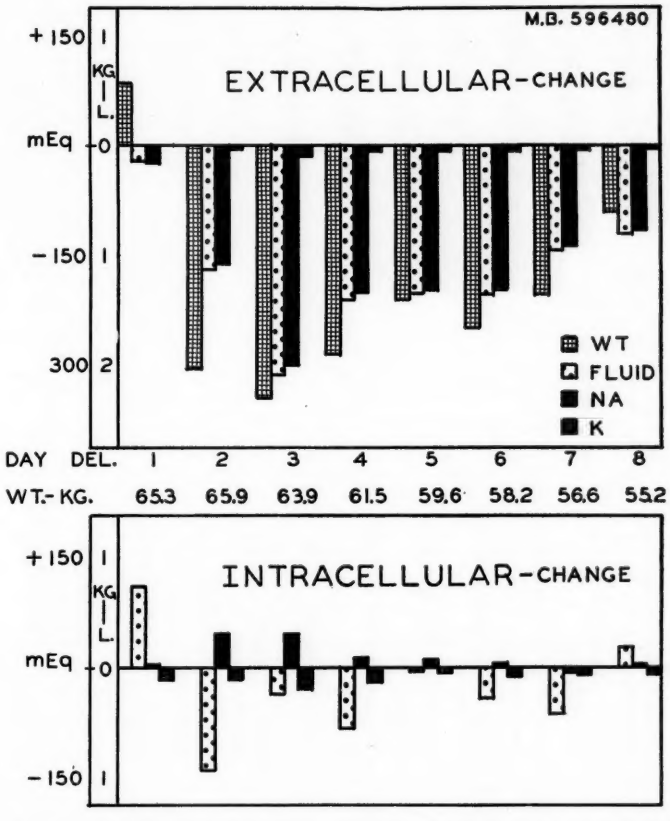

Fig. 7.—Case 2. Daily changes show increase in extra and intracellular water on first day due to hypertonic dextrose solution, but decrease of extracellular Na. Thereafter, the extracellular compartment lost most of the water and sodium while the intracellular compartment lost water and potassium, but gained sodium.

Case 3 was a 17-year-old Negro primigravida, who had been treated in a city clinic from August 17 to November 25, during which time she gained 14 kilograms, with a final 3 plus edema, a blood pressure of 140/100, and a 4 plus proteinuria. She was at term about March 20, 1950, but was admitted to the hospital on Nov. 25, 1949, because of the pre-eclampsia, pyelonephritis, and ileus with vomiting. She was treated by parenteral fluids, including 1,800 ml. of ⅙ molar sodium lactate solution to alkalize the urine, and penicillin, streptomycin, and gastric suction. Despite the administration of adequate amounts of parenteral fluids, the hematocrit on admission was 52 per cent, and 48 hours later was 54 per cent, with a hemoglobin of 16.7 Gm. per 100 ml. of blood, where it remained for another 24 hours. The patient was given 100 Gm. of serum albu-

TABLE VI. CASE 3. ECLAMPSIA, PYELONEPHRITIS, ILEUS

1949 DAY	WEIGHT (KG.)	EDEMA	Hb. (GM. %)	SERUM PROT. (GM. %)	SERUM ALB. (GM. %)	SERUM (MEQ.) Cl	Na	K	VOLUME (L.) BLOOD	SERUM	REMARKS
8/17	58.6										
11/22/49											
9 Admission		+++									
8	72.6	++++	15.0	4.9	--	103	123	5.1			Sodium lactate ⅙ M-1,800 ml.
8			15.0	4.8	2.0	103	123	5.1			
7	74.9	++++	14.5	4.6	1.8	94	110	3.8			
6		++++	16.7	5.2	2.6	97	97	--			
5	76.5	+++	15.6	5.0	1.9	83	114	3.7	4.60	2.18	Serum albumin 100 Gm.
			10.4	5.5	4.1	84	110	3.8			
4	73.1	++	12.2	4.5	2.6	97	118	3.7			
2		++	13.3	5.2	--	98	117	4.2			
1	71.6	++	12.9	4.6	2.2	98	119	3.9			Plasma 1,200 ml.
Delivery A. P.	71.1	++	10.4	5.0	2.4	103	113	4.2			Plasma 1,200 ml.
P. P.	67.5		9.5	5.5	2.6	99	113	3.8			(Total protein—144 Gm. from plasma)
			10.6	6.1	2.5	98	117	3.8	3.32	2.13	
1	68.4	++	8.0	4.6	2.2	101	122	4.2			
3		++									
4	64.0	++	6.8	4.8	1.9	97	112	4.2			
6		++	7.1	4.8	1.7	103	121	4.1			
7		++	8.2	5.1	1.8	102	118	4.4			
10	59.0	+	7.1	5.1	1.8	100	120	4.1			
11		+	7.9	5.8	1.7	98	118	4.0	3.12	2.50	
12 Discharge	58.0										
				Rectus muscle, fat free, wet			39	74			
				Skin			108	8			

min, which caused a prompt dilution accompanied by some clinical improvement. Several days later, the patient was given 1,200 ml. of plasma to promote a still further dilution, and this injection was repeated on the next day. The following day, the hematocrit was 36 per cent, and hemoglobin 10.6 Gm. per 100 ml. of blood. The serum protein and albumin had increased slightly as shown in Table VI. The serum chloride on admission was normal, and although fluids containing NaCl were given to the patient, the serum chloride steadily decreased.

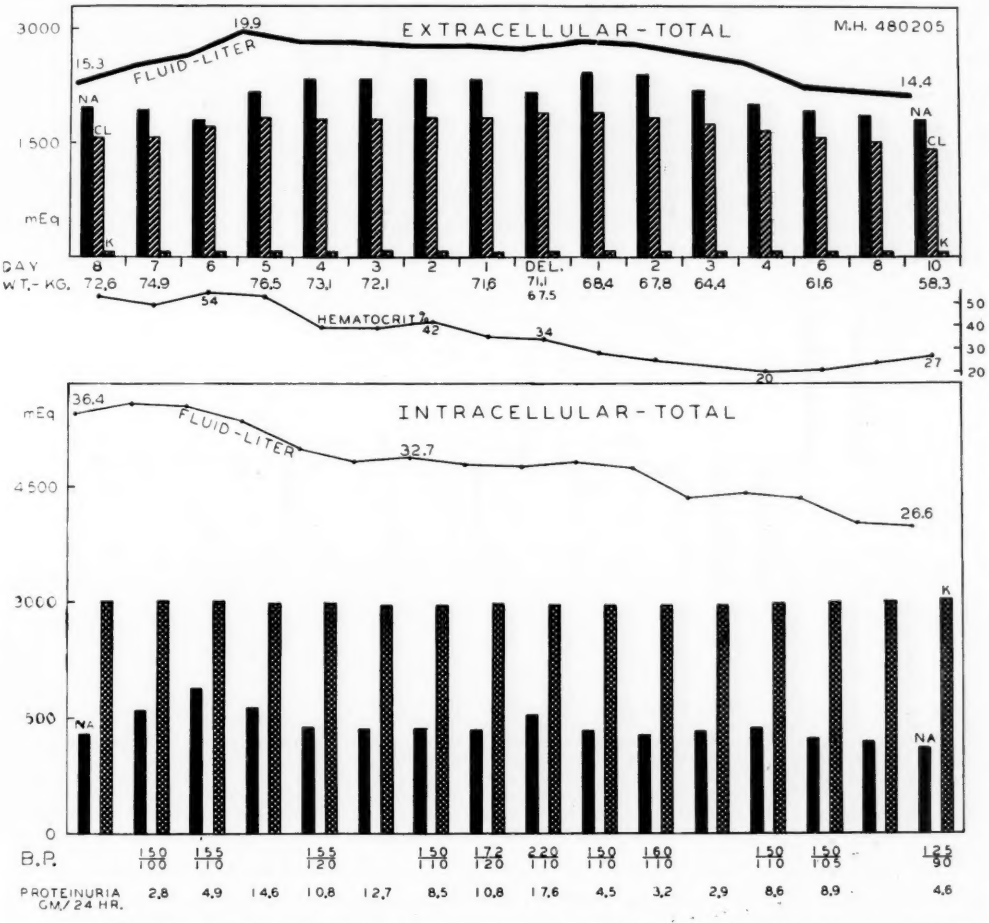

Fig. 8.—Case 3. (M. H. No. 38) Eclampsia. Shows hemoconcentration in an edematous patient with increase in extracullular water, Na, and Cl due to parenteral fluid, serum albumin, and plasma, culminating in eclampsia. A decrease in fluid occurred in both compartments post partum with decreases in Na and Cl in extracellular fluid.

The serum sodium was definitely below the normal concentration throughout the course in the hospital and was even lower, 113 meq., at the time when convulsions, marked hypertension, and coma occurred. This would seem to indicate that pre-eclampsia-eclampsia is not due to a primary sodium intoxication, that possibly the water retention is first, or, what is more likely, that the abnormal relations of water and electrolytes between plasma, interstitial and intracellular fluid compartments are the primary disturbance. Because of the marked increase in blood pressure we wished to determine how the pregnancy should be terminated. On the way to the delivery room, the patient had one convulsion and, although the usual sedative drugs were given, another convulsion occurred

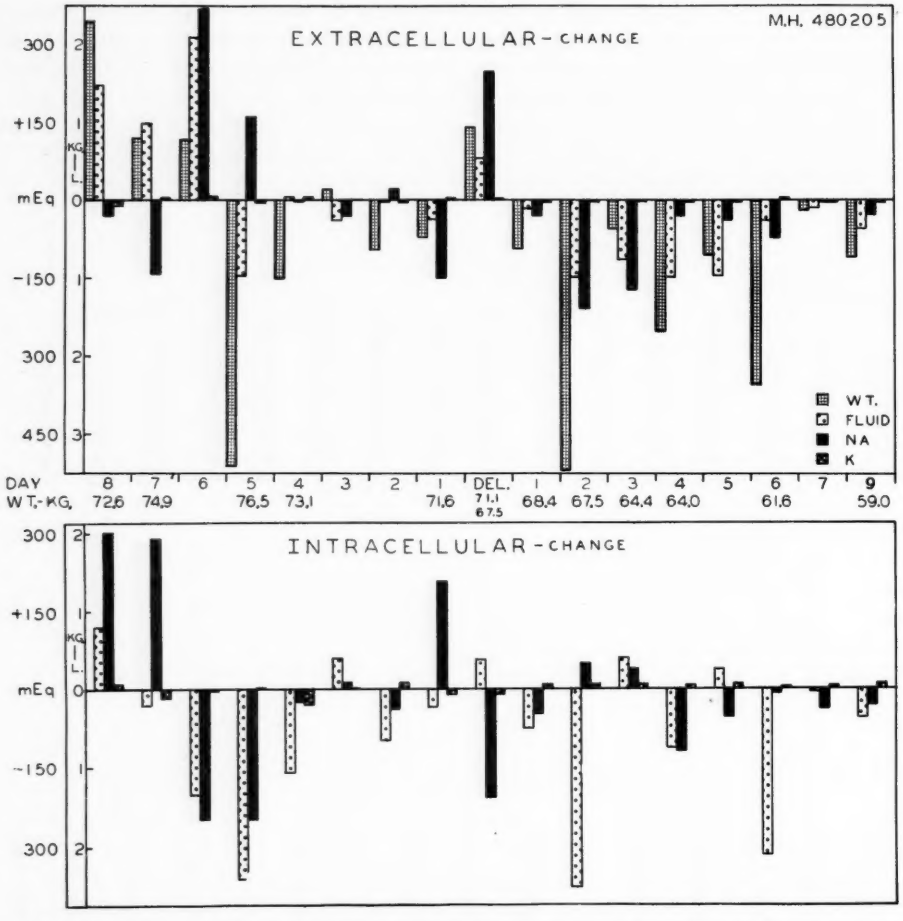

Fig. 9.—Case 3. Daily changes show increases in weight, extracellular Na and water and intracellular Na, after the sodium lactate and NaCl solution on day −5. After the serum albumin, the loss in weight seems to be associated with minimal Na changes. Post partum, the greatest losses are of extracellular sodium and intracellular fluid.

before delivery. Because the cervix was closed, a cesarean section was performed, with the delivery of a live 1,400 gram fetus. The patient had four antepartum convulsions and none subsequently. At the time of the operation subcapsular hemorrhages could be seen in the right lobe of the liver.

Fig. 8 shows the marked changes in the total fluid and electrolyte in both compartments, there being an increase in extracellular fluid of 4.6 L. with increases in sodium and chloride, amounting to 10 and 16 per cent, respectively. These increases occurred despite the low serum sodium values which were still present, even at discharge. The intracellular fluid volume decreased 9.6 kg. with initial increases in sodium amounting to 594 meq., 45 per cent, and at discharge the intracellular sodium was approximately 200 meq. less than on admission. The changes in the osmotic activity of the base are tremendous, before delivery 112 meq. of base was osmotically inactive, and after delivery 299 meq. of base was inactive, a total of 411 meq.

Fig. 9 shows the changes in extra- and intracellular water and electrolyte concentrations. They are of great magnitude in short periods of time and were finally associated with typical eclampsia. There were marked increases in extracellular water and sodium during the first three days. Thereafter, there was

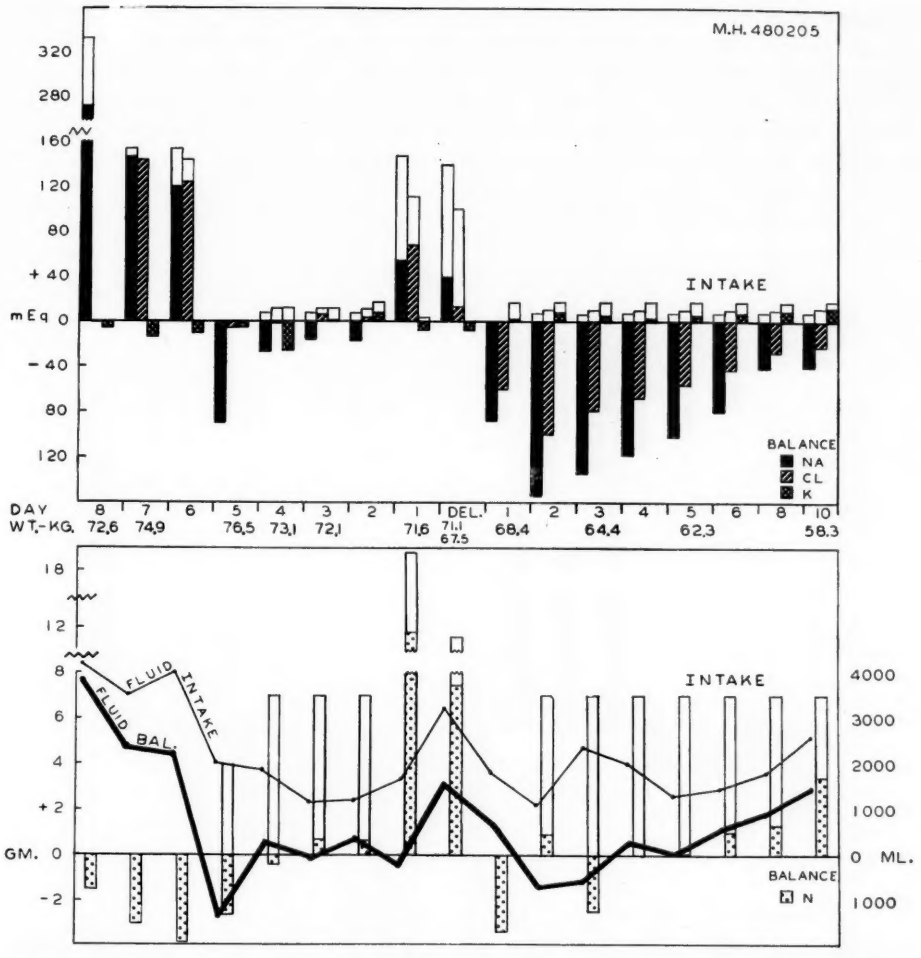

Fig. 10.—Case 3. Balance. Note initial fluid and sodium retention with nitrogen loss after intravenous fluids (sodium lactate, NaCl solution, and plasma). On day -5 serum albumin caused an appreciable loss of Na, but after blood plasma, the Na and N balances were positive on day -1 and delivery. The Na and Cl losses post partum were associated with even a more pronounced weight loss.

a steady decrease in extracellular fluids and sodium. Although the serum albumin caused a marked increase in plasma volume, it had very little effect on the interstitial and intracellular fluids and electrolytes. The plasma injection again caused an increase in the extracellular water and sodium.

The balance studies, Fig. 10, are of extreme interest because they show an initial retention of Na and Cl; but they are negative post partum even though the serum values were always subnormal.

The patient was delivered in 1950 and again in 1951 without any evidence of toxemia. Addis counts and urea clearances were within the normal range in the subsequent pregnancies.

Case 4 was a 27-year-old white primigravida, at term on Aug. 3, 1949. On July 13 there was a 2 plus proteinuria, with blood pressure of 120/100. On July 20 she had gained 2 kilograms, the blood pressure was 150/110, edema 1 plus, and proteinuria 3 plus. On July 22 she had lost 0.4 kilogram but the blood pressure was 175/120 with 1 plus edema and 3 plus proteinuria and she was admitted to the hospital (Table VII). The sodium intake of the diet was

consistently below 300 mg. but the potassium averaged 2.5 Gm. (Fig. 11). During the first 48 hours, the patient lost 1.1 kilograms but a water clearance caused an increase in weight of 0.2 kilogram. On three successive days the patient was given 1,000 ml. of a 2.5 per cent NaCl solution intravenously and 7 Gm. of NaCl in enseals by mouth, making a total intake for three days of 96 Gm. of NaCl or 1,665 meq. of Na. There was a 2.6 kilogram increase in weight with no change in edema but a marked increase of the blood pressure to 190/130 and an increase in the proteinuria to 10.6 Gm. per 24 hours. The pregnancy

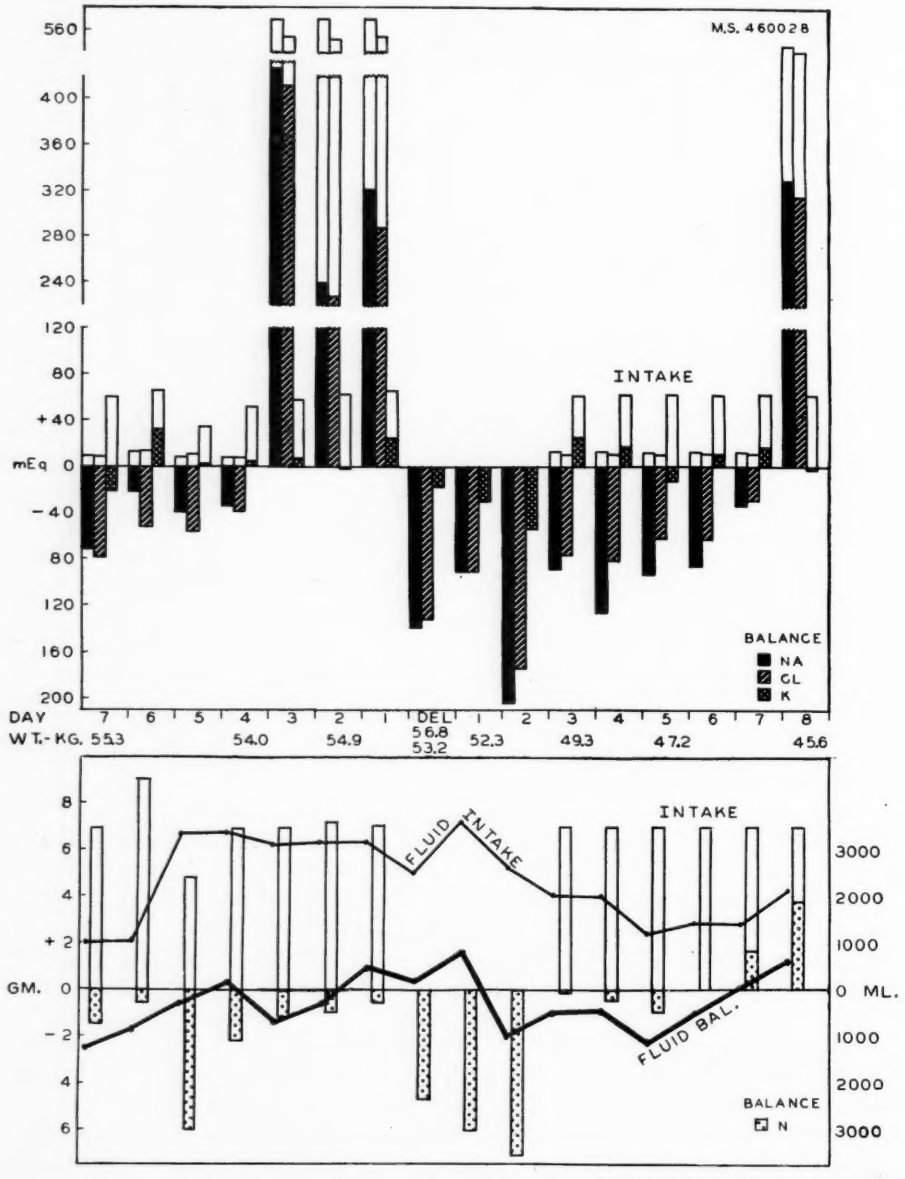

Fig. 11.—Case 4. (M. S. No. 101). Pre-eclampsia. Balances: with a low intake of Na and Cl the loss of Na, Cl, and weight on the -7 to -3 days is small. On -3, -2, and -1 days, a 32 gram NaCl load per day caused a marked positive balance of Na and Cl, with a 2.8 kilogram (450 meq. Na/kilogram) weight increase for the three days. The water, Na, Cl, and K balances were strikingly negative after delivery (105 meq. Na/kilogram weight loss).

TABLE VII. CASE 4. SEVERE PRE-ECLAMPSIA, LOW SODIUM BUT HIGH POTASSIUM DIET

1949 DAY	WEIGHT (KG.)	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	HEMATOCRIT (%)	SERUM PROTEIN (GM. %)	SERUM (MEQ.) Cl	Na	K
7 Admission	55.33	+	170/105	3.7					
6	54.2	+	140/90	4.9	39	5.6	102	135	5.0
4	53.98	+	150/110	4.6	41	5.3	96	129	4.9
2	54.91	+	150/110	7.3	37	5.4	103	136	5.1
1	55.4	+	170/110	10.6	37	5.2	98	135	4.7
Delivery A. P.	56.81	+	190/120		38	5.4	103	137	4.9
P. P.	53.2		145/100						
1	52.29		166/95	2.5	31	4.4	94	136	4.7
2	50.64	0	160/100	2.0					
3	49.3	0	150/100	3.0	30	4.9	101	138	4.9
5	47.22	0	140/100	2.8					
6	46.5	0	140/90	1.6	30	5.3			
8	45.6		130/90	1.9	36	6.2	98	132	6.0
10	46.4		130/85	2.1	33	5.6	103	137	4.5
11 Discharge 8/9/49	45.04		130/90		35	6.0	99	123	4.5
41					41	7.4		134	5.5
					42	7.0			
					Rectus muscle, fat free, wet			41	87
					Skin			111	20

DAY	VOLUME (L.) BLOOD	SERUM	LEG	E. C. F.
4 ante partum	360	2.12	9.7	19.2
Delivery	2.94	1.82		21.7
10 post partum	3.20	2.14	8.9	13.8

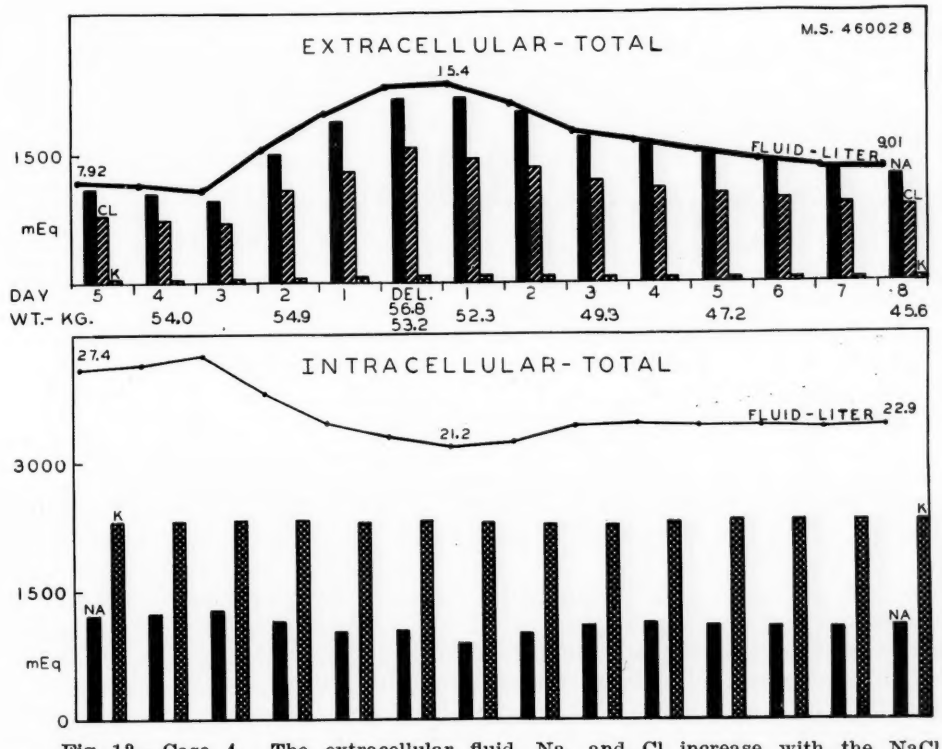

Fig. 12.—Case 4. The extracellular fluid, Na, and Cl increase with the NaCl load before delivery, and the intracellular fluid and sodium decrease almost proportionately. Post partum; the extracellular fluid, Na, and Cl decreased, accompanied by an increase of intracellular water and sodium.

was terminated by cesarean section. During the first three hospital days the patient excreted a maximum of 48 meq. of sodium per day, but the balances were all negative. On the three days of the sodium chloride test the maximum urine excretion was 330 meq. During the three days the patient was given 1,665 meq. of sodium, she excreted only 715 meq. and retained 950 meq. Following delivery there was an immediate increase in the sodium excretion ranging from 100 to 200 meq. per day. The maximum concentrations occurred during the first 72 hours, when the patient received only water by mouth and intravenous injections of 20 per cent dextrose solution.

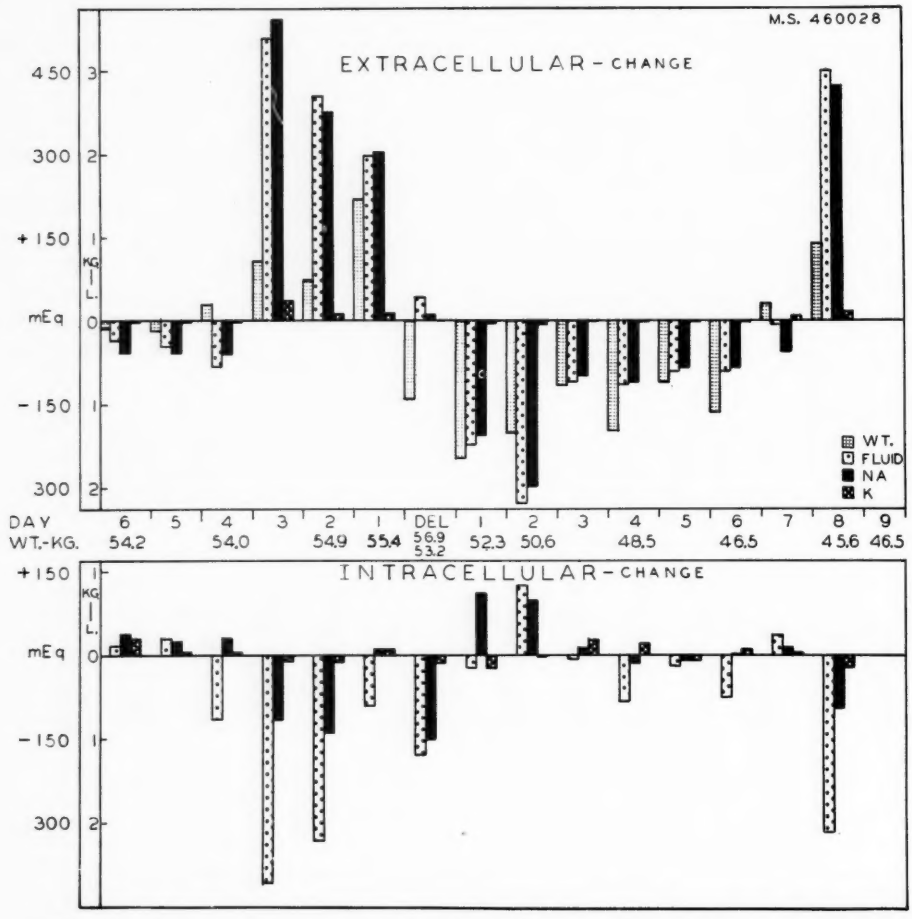

Fig. 13.—Case 4. With a low Na and K diet the changes are small; with a salt load the extracellular fluid and Na increased, accompanied by a decrease of intracellular fluid and Na. After delivery the extracellular fluid and Na decreased markedly with a loss in weight. The response on day 8 to 25 grams NaCl seems to resemble the antepartum response.

Fig. 12 shows the total changes in the body compartments. During the first three days there was a decrease in the extracellular fluid, sodium, and chloride. Sodium chloride injections resulted in an increase in weight of 2.6 kilograms, an increase of 7.2 L. of extracellular fluid, a decrease of 6.4 L. in intracellular fluid, and a decrease of 200 meq. of sodium. Thus, the sodium chloride injection resulted in a 128 per cent increase in the extracellular sodium and an increase of 127 per cent in chloride. The extracellular fluid increased 118 per cent and the intracellular fluid decreased 25 per cent. Intracellular sodium

decreased 13 per cent and the osmotically active base which had amounted to 71 meq. in the first 48 hours now amounted to 456 meq. After delivery, the extracellular volume decreased, the sodium decreased from a maximum of 2,195 to 1,500 meq. and chloride from 1,571 to 1,071 meq. After delivery there was a 6.8 kilogram loss in weight, and a 5 L. loss in extracellular fluid. There was a marked loss in extracellular sodium and chloride but the values were still higher than on admission. There was an additional change of 840 meq. of base to an osmotically inactive phase.

Fig. 13 shows the extra- and intracellular changes and it is apparent that the patient was improving until she received the sodium chloride by oral and intravenous routes. There was a marked increase in extracellular fluid, sodium, chloride, and potassium. There was a marked decrease in intracellular fluid and sodium. During this phase of sodium retention a large amount of base became osmotically inactive. Presumably, had the patient been thirsty enough to drink more water, these marked changes in the body compartment might not have occurred. However, there was sufficient excess base to contribute 3.2 L. of extracellular fluid which would have necessitated further shifts between the cell and the interstitial fluid. All evidence indicates that the normal body has a large safety factor to protect against excess or lack of water as well as excess or lack of electrolytes. It seems that the inactivation of the excess base by whatever method or to whatever depot it went caused the least disturbance to the body, although the patient's blood pressure and the proteinuria increased markedly. After delivery, there was the usual readjustment with decreases in extracellular water, sodium, chloride, and potassium. Intracellular fluid changes were minimal with the usual increase in intracellular sodium. The injection of 1,000 ml. of a 2.5 per cent sodium chloride solution, 427 meq. of Na, on the eighth day of the puerperium, resulted in an increase on weight of 0.2 kilograms, in extracellular fluid of 3 L., 33 per cent, and in the extracellular sodium, chloride, and potassium. Again there was a decrease of 2.1 L. of intracellular fluid and sodium and a marked increase in the amount of inactive base.

A repeat cesarean section on May 6, 1952, resulted in a normal, 3,305 gram baby. The patient had numerous tests on both admissions to the hospital, and we believe she had a severe pre-eclampsia in the initial pregnancy and the second pregnancy was normal.

TABLE VIII. CASE 5. HYPERTENSIVE DISEASE, LOW SODIUM AND POTASSIUM DIET

1950 DAY	WEIGHT (KG.)	EDEMA	BLOOD PRESSURE	PROTEINURIA (GM. PER 24 HR.)	HEMATOCRIT (VOL. %)	SERUM PROTEIN (GM. %)	SERUM (MEQ.) Cl	Na	K
7 Admission	65.61	++	150/100	0.5	35	6.3	102	138	4.7
6	65.06	++	140/100	0.5	35	6.8	98	140	5.7
4	64.66	++±	140/90	0.2	33	5.8	104	134	4.5
3	65.46	+++	150/90	0.6	32	5.8	102	134	4.3
2	66.11	+++	156/110	0.7	32	6.2	104	139	4.2
1	66.46	++	180/110	0.6	34	6.2	104	135	4.4
Delivery				1.4					
P. P.	59.66	++	160/108						
1		+	150/90	0.3					
2	55.11	0	160/90	0.5					
4	55.21		150/90		34	6.5	100	137	5.2
6			130/80		33	6.4	99	139	5.2
9	54.1		150/100						
36					39	7.2			

	VOLUME (L.)			
DAY	EXTRACELLULAR	BLOOD	SERUM	LEG
6 ante partum	19.2	4.97	3.23	14.0
6 post partum	13.9	3.52	2.33	12.9

Case 5 was a 17-year-old white primigravida, at term on June 26, 1950. She was first seen on Nov. 25, 1949; by May 31 she had gained 15 kilograms, had a 1 plus proteinuria, a 1 plus edema, and blood pressure of 165/115. She was placed on a low sodium and potassium diet, and on June 9, although she had lost 1 kilogram and her blood pressure was 145/90, with a 2 plus

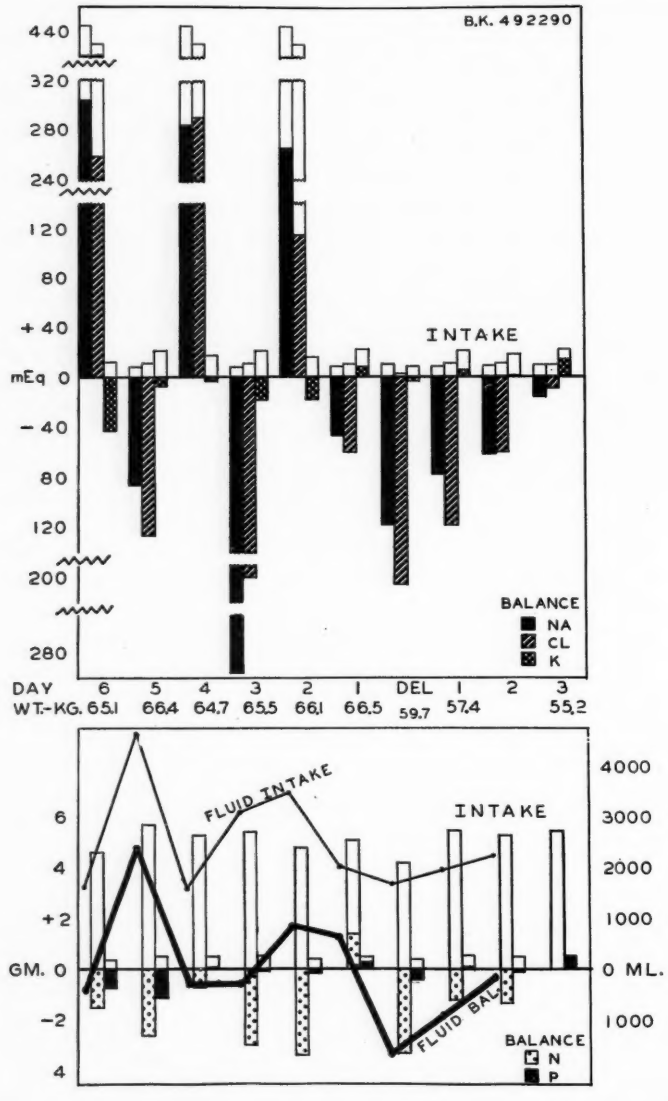

Fig. 14.—Case 5. (B. K. No. 109). Hypertensive disease. Balances show that after each intravenous injection of 25 grams NaCl on every other day, there is a retention of Na and Cl which is compensated on the following day. The 4.5 kilogram weight loss post partum has associated with it 60 meq. Na per kilogram.

edema, she was admitted to the hospital (Table VIII). She had the usual examinations of the retina, urea clearance, Addis count, etc. A water clearance and three test doses of 1,000 ml. of a 2.5 per cent solution of NaCl were given on June 11, 13, and 15. She was able to concentrate sodium, and two sub-

sequent hypertensive pregnancies confirmed our diagnosis of hypertensive disease. She went into labor spontaneously on June 17 and delivered a 3,770-gram baby without any difficulty.

The loss at delivery amounted to 6.8 kilograms and, in addition, the patient lost 3.1 kilograms. Fig. 14 shows relatively large excretions of Na which increased after the test injection. The nitrogen loss was comparatively small, when compared with previous balances. At the end she had lost 584 meq. of osmotically active base.

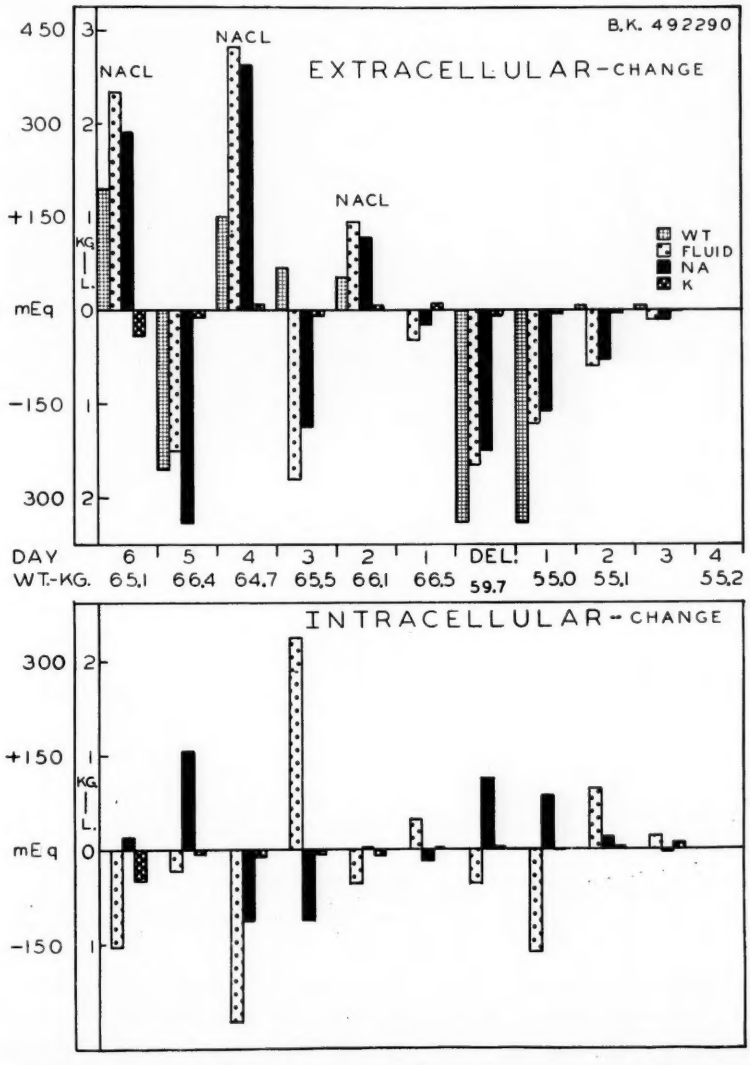

Fig. 15.—Case 5. The weight, fluid, and Na increase with the NaCl load and decrease on the following days when nothing was given. After five days the change was a 0.9 kilogram gain in weight with retention of 346 meq. of Na and 279 meq. of Cl. Post partum: the weight, fluid, and Na decrease in the extracellular fluid with a gain in the intracellular Na.

Fig. 15 shows the increase in extracellular fluid, sodium, and chloride due to the test injection; these increases amounted to approximately 30, 20, and 27 per cent, respectively. There were marked changes in the extracellular fluid, chloride, and sodium, and essentially reverse changes in the intracellular

sodium. The patient was able to excrete the excess sodium and chloride ions, and the base that could not be excreted became osmotically inactive. The data show clearly that where there is little or no impairment of water and sodium excretion, although intravenous injections of NaCl solution produced marked changes in intra- and extracellular compartments, these are transient and are rapidly corrected.

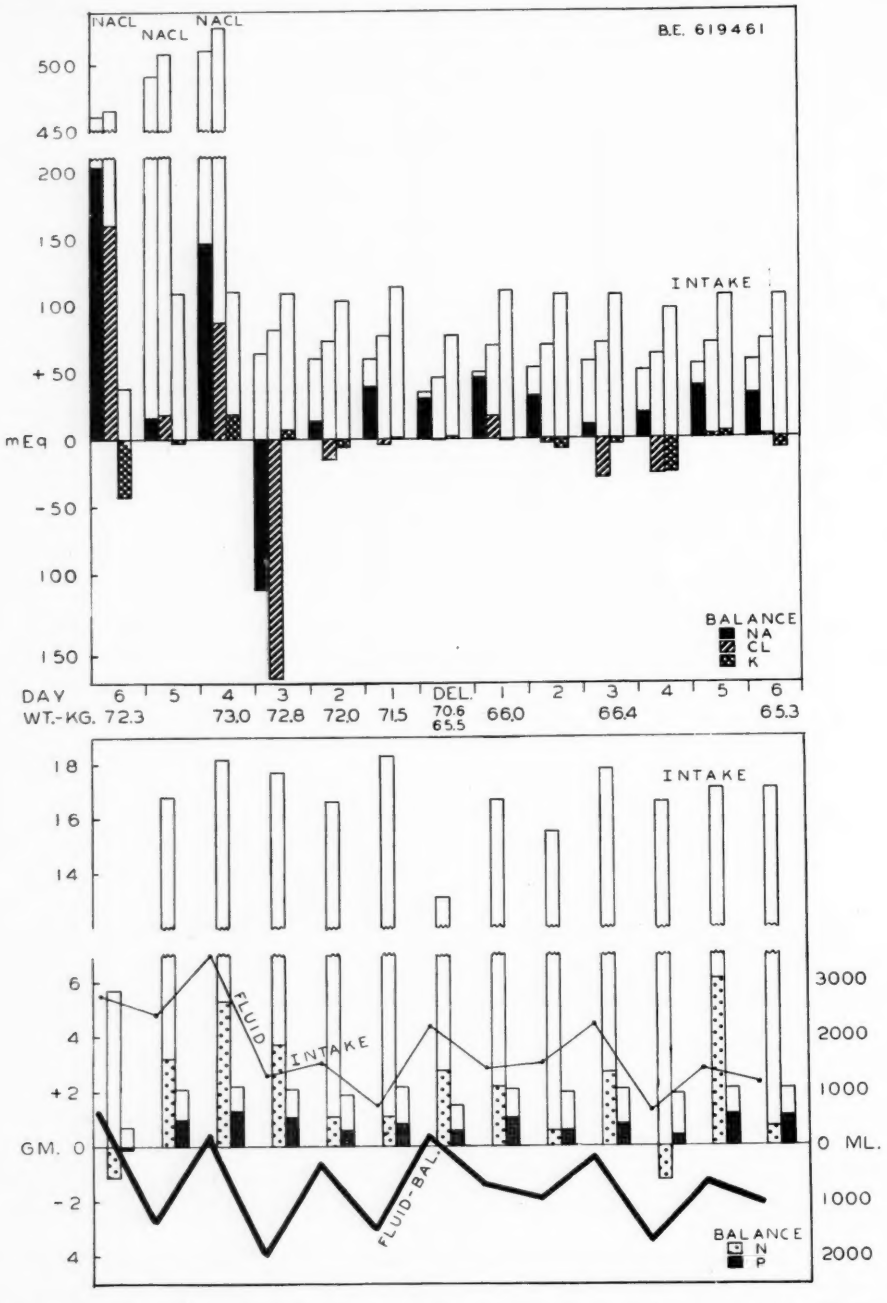

Fig. 16.—Case 6. (B. E.) Normal pregnancy. Seventy-five grams of NaCl caused only 0.5 kilogram gain. The balances for Na, N, and P were positive both ante and post partum. Balances for K and Cl were equal or slightly negative.

Case 6 was a 17-year-old white primigravida who had a normal pregnancy. She was on a weighed regular diet and was given three intravenous injections of 1,000 ml. of 2.5 per cent NaCl solution (427 meq. of sodium) (Fig. 16). She had a positive Na and Cl, but negative K balance ante partum, retaining 300 meq. Na. Post partum, 172 meq. of Na were retained, while K was lost. There was a huge nitrogen retention. The delivery loss amounted to 5 kilograms and the antepartum weight loss in six days was 1.8 and post partum there was a gain of 0.4 kilogram. Fig. 17 shows the increases in extracellular water, Na, and K due to the NaCl injections and the decreases in the intracellular. Although there are fluctuations, they are of less magnitude than in the pre-eclamptic patients.

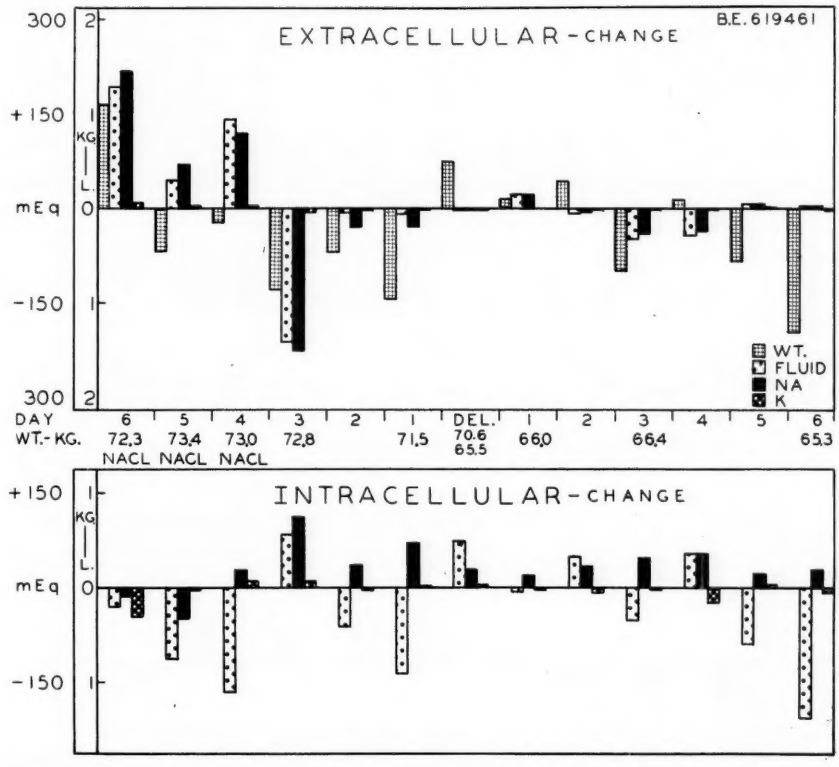

Fig. 17.—Case 6. The increase in extracellular fluid and sodium was compensated during the 3 days following the salt load. Noticeable about this normal pregnancy is the small variable change in weight, extra- and intracellular Na and K.

Case 7 was a 17-year-old white primigravida who had a normal pregnancy. She was on a weighed regular diet (Fig. 18). Both ante and post partum, the Na and P were always positive in small amounts. The Cl and K were positive or negative in small amounts. Nitrogen was retained in large amounts. Fig. 19 shows the minimal changes in the extra- and intracellular compartments. They differ markedly in both Cases 6 and 7 from those seen in pre-eclamptic patients.

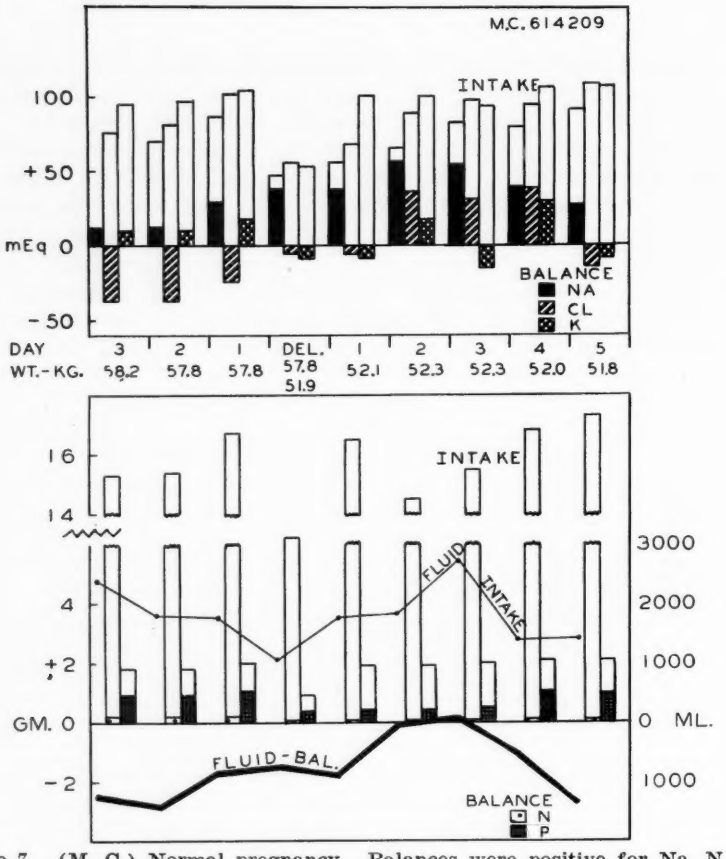

Fig. 18.—Case 7. (M. C.) Normal pregnancy. Balances were positive for Na, N, and P, but borderline or negative for K and Cl.

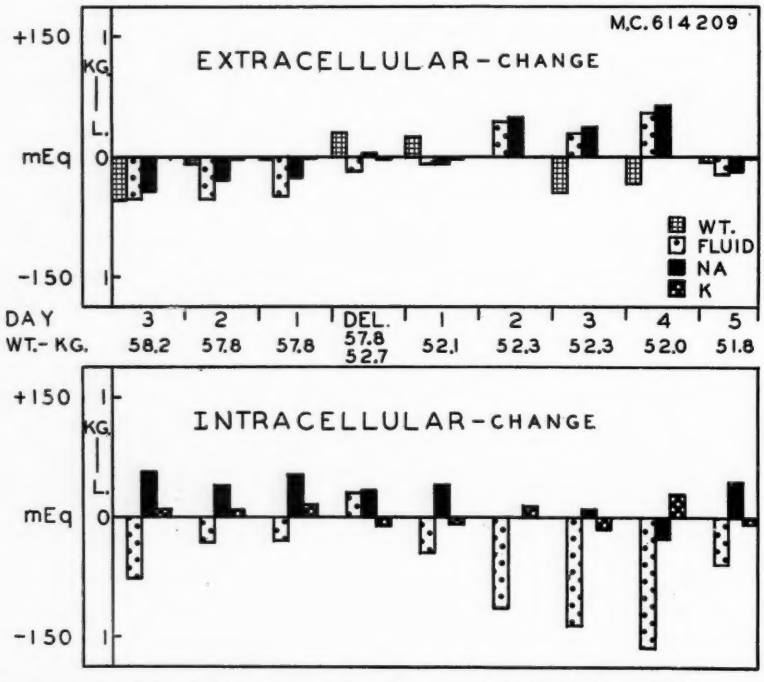

Fig. 19.—Case 7. The daily changes in extra- and intracellular fluid were minimal. Note increase in Na in intracellular, but loss of fluid.

Comment

Lambiotte-Escoffier and associates[20] in 1953 studied seven patients with pre-eclampsia, two normal nonpregnant women, and two normal pregnant women, using inulin and sodium[24] for their respective spaces and antipyrene for total body water. They concluded that the pre-eclamptic patients had a consistently expanded antipyrene and sodium space, but normal inulin space. They thought their data indicated that pre-eclampsia is characterized by increased intracellular penetration of sodium and water. They quoted Rossenbeck (1931), to the effect that direct tissue analysis had revealed significant increases in muscle sodium during pregnancy and enormous increases in eclampsia. An extensive unpublished study of ours shows that the sodium content of the rectus and gastrocnemius muscles is increased in normal pregnant patients but is *not* increased in patients with pre-eclampsia-eclampsia or hypertensive disease.

Seitchik and Alper[27] in 1954 used antipyrene and mannitol for their studies and concluded that the increase in extracellular fluid volume in normal pregnant patients is proportional to the gain in lean body tissue. Excessive water retention in pre-eclampsia or in edematous nontoxemic patients occurred in the extracellular space. There was no evidence of excessive intracellular water retention.

Hutchinson and co-workers[14, 15, 16] in 1954 used deuterium oxide and stated that there was an absolute rise in total body water and total solids in normal pregnant patients. The water turnover rates for pre-eclamptic patients were lower than for normal pregnant patients, while hypertensive patients had rates which were either faster than normal or within the normal range. The authors suggested that the water turnover rate might eventually be used as a diagnostic and prognostic procedure.

There have been several studies in which water, dextrose, or sodium chloride solution were injected intravenously in experimental animals, and the various compartments and their water and solute concentrations were determined. One of the latest is by Leaf and associates[21] in 1954, who injected a 2.5 per cent solution of dextrose intravenously into dogs in whom both ureters had been ligated or both kidneys removed. Their findings indicated that in vivo the great majority of body cells adjust to acute dilatation of the extracellular fluid by a net movement of water into the cells, so that the administered load is distributed evenly over the entire body water content.

All experiments, whether they involve the injection of dextrose solution, of hypo-, iso-, or hypertonic saline solution, indicate that there is an adjusting mechanism in the normal body which causes a retention of water if the plasma and interstitial fluid are hypertonic, but if they are hypotonic, it causes an increased tubular reabsorption of sodium and chloride ions as well as the excretion of a dilute urine. Considerable time may be required for adjustment if large amounts of water or solutes are used. It is a well-known fact that it is extremely difficult to cause marked disturbances in the extracellular and intracellular fluid compartments. Thus van Goidsenhoven and his col-

laborators[13] in 1954 reported upon a group of patients with gastric ulcer, some of whom took as much as 150 Gm. of sodium bicarbonate daily for as long as three weeks. There were some increases in body weight; some patients showed slight edema as well as a slight hypertension, but there were no other symptoms or signs, and as soon as the medication was stopped, the body rapidly returned to normal.

Increased venous pressure in the lower extremities or in the upper half of the body causes a retention of water and NaCl. Pearce and Newman[24] in 1954 reported that in the normal human subject undergoing moderate diuresis, quiet standing resulted in a marked decrease in sodium, chloride, potassium, and water excretion, as compared with control measurements in the supine position. If the legs were wrapped with elastic bandages before the orthostatic position was assumed, the depression of salt excretion was inhibited.

All experiments indicate that there are individual differences. Stewart and Rourke[29] studied the effects of large intravenous infusions on the body fluids. One patient was given 27 L. of 0.9 per cent saline solution intravenously in 96 hours without the development of any symptoms or signs. There was a marked retention as indicated by the increase in weight, decrease in hematocrit, plasma protein, and the increase of plasma and extracellular fluid volumes. The injection was at a fairly constant rate and there was a retention of sodium until the fourth day when more sodium was excreted than was injected and, had the experiment been continued, presumably the patient would have slowly regained balance.

Another patient was given 7 L. of 5 per cent dextrose solution intravenously in 36 hours and became comatose. There was a slight increase in plasma volume and in extracellular fluid volume, although the weight decreased during the injection. The coma was undoubtedly due to the marked drop in serum sodium and chlorides and decrease in intracellular volume and electrolytes. The patient recovered.

The changes in extra- and intracellular fluid and electrolytes occurred in our patients who survived. They are of greater magnitude in anuric patients and show even greater distortion in patients who died. Our studies show that, although there has been a greater retention of sodium and chloride ions, there has been an even greater retention of water. A similar observation has been made repeatedly in patients recovering from heart failure.[19, 29] It does not follow that the pre-eclamptic patient primarily had a water retention and secondarily a sodium chloride retention, although this theory must be kept in mind. Despite the fact that, irrespective of the percentage of body weight which we assume to be extracellular or even determine as extracellular, the concentration of sodium and chloride ions is not abnormally high. We have unpublished studies which show that in normal pregnant patients there is a significant increase in sodium ions in the rectus muscle, but in pre-eclamptic and hypertensive patients, there is *no* increase; instead, the concentrations are similar to those found in the rectus muscle from nonpregnant women. Thus, in pre-eclampsia, although there may have been hypertonic body fluids at various times, when the patient has reached a stage with signs and symptoms, the serum electro-

lyte levels are not different from normal and both extra- and intracellular fluids are in balance, but the intracellular sodium is lower than that of the normal pregnant patient. Since all body functions are dependent on intracellular concentrations of water and electrolyte, it is obvious why these patients have the various signs and symptoms, the specificity of which will depend on the particular organ or organs most involved. Thus, if the motor cortical areas of the brain are involved, there will be convulsions; if sensory areas, coma, etc. If the kidney is involved, there will be decreased blood flow with a diminution of urine, marked changes in the tubular function, as well as an augmentation of the various symptoms and signs associated with renal impairment.

The serum sodium and chloride concentrations are increased for some hours after the injection of hypertonic NaCl solution, but they soon return to the preinjection value, thus indicating that either fluid has been obtained from the cells or sodium has gone into the cells and has become presumably osmotically inactive.

An intravenous injection of hypertonic dextrose solution in normal subjects causes a hemodilution with osmolar changes in electrolytes and freezing points proportional to the blood sugar elevation but in an hour after injection the values are back to normal. In pre-eclamptic-eclamptic patients the dilution is greater and usually persists in varying degrees, as demonstrated by Schwarz and Dieckmann[26] in 1929.

Before delivery, a low sodium and potassium intake, forcing fluids, diuretics, etc., have only a transient effect in promoting a negative sodium balance, but within 12 to 48 hours after delivery there is a tremendous loss of sodium, chloride, and water, and, to a lesser degree of potassium, nitrogen, and phosphorus.

Could the sudden increase in urine excretion of water and of the sodium ion and undoubtedly other substances be the result of hormone effect or mechanical; that is, could it be due to the return of the abdominal and inferior vena cava pressure to normal, or both? It seems to us that the alteration is primarily a mechanical one. Unconsciously, we are probably influenced by the fact that if there had been a primary disturbance in the posterior lobe of the pituitary gland and/or the cortex of the adrenal in the pre-eclamptic or eclamptic patient, it is hard to understand why one or both of these glands do not become abnormal in subsequent pregnancies with a recurrence of the pre-eclampsia or eclampsia. It is true that our criteria for this condition are not well established, but everyone[11] who has studied a large number of toxemic patients through several pregnancies is cognizant of the fact that typical pre-eclampsia or eclampsia rarely, if ever, recurs. Furthermore, a patient may have had several normal pregnancies and then have typical pre-eclampsia or eclampsia due to either multiple pregnancy or polyhydramnios. However, subsequent pregnancies are again normal. These observations seem to support some mechanical disturbance, which may be the increased intra-abdominal and inferior vena cava pressure.

In a few patients, we seem to have been able to eliminate the excess water before delivery, as judged by a failure to lose weight after delivery, but *we have not been able to cure a single pre-eclamptic patient without delivery.* Possibly, if we had a sufficiently long time for the body to readjust water and electrolytes in the intracellular compartment, the patient could be cured without delivery.

The daily postpartum changes in the extracellular compartment show a consistent decrease in the water, sodium, and chloride for patients who have pre-eclampsia, eclampsia, or hypertensive disease. The changes are most marked in the pre-eclamptic and eclamptic patients. The intracellular compartment shows a slight but consistent decrease in potassium and a considerable increase in sodium in pre-eclampsia-eclampsia, again emphasizing the marked disturbance which has been present, and which again is more marked in the pre-eclamptic-eclamptic patient.

Patients prior to 1948 were on a weighed diet which contained 0.4 Gm. of sodium, 0.6 Gm. of chloride, and 3.3 Gm. of potassium, 65 Gm. of protein, and 1,570 calories. Since 1948 the diet has contained 0.2 Gm. of sodium, 0.4 Gm. of chloride, 1.0 Gm. of potassium, 47 Gm. of protein, and 1,530 calories. On this diet all patients showed negative balances for sodium and chloride and usually potassium before delivery. The normal pregnant and hypertensive patients showed greater antepartum losses than the pre-eclamptic patients in whom the loss of sodium was *small.* Beginning somewhere between 12 and 48 hours after delivery, there is a tremendous increase in the loss of sodium and chloride from the extracellular fluids. This persists for a varying number of days and then begins to decrease, but even at ten days, it is still negative. We now know that these patients will have to be followed for probably twenty days after delivery before the cellular electrolyte physiology is back to normal. We have studies in progress to determine more exactly the precise time at which the increase in sodium excretion begins.

A study of the total changes in extra- and intracellular compartments of water, sodium, chloride, and potassium indicates that all patients whose weight or whose diet is changing experience the changes just mentioned. Short-term experiments available in the literature, as well as our own, and animal experimentation, show that the normal body has a tremendous reserve capacity for handling large amounts of water and/or of electrolytes given orally or intravenously and also has a tremendous capacity to compensate for a lack of water, such as occurs in dehydration, or a lack of essential electrolytes such as occurs after excessive sweating, a restricted sodium, potassium, or chloride diet, etc. Our data show that the total compartmental changes are much greater in the pre-eclamptic and eclamptic patient in per cent and require a longer time for adjustment. This is seen in the postpartum period in Cases 1 and 2 and in the antepartum and postpartum periods in Cases 3 and 4. It is also worth noting that ammonium chloride caused only a transient increase in sodium excretion, and has little effect on the intracellular compartment.

Case 5 was diagnosed as pre-eclampsia, but the patient's ability to concentrate sodium in the urine and the failure of her signs to increase in severity after three injections of sodium chloride made us question the diagnosis. Two subsequent pregnancies indicate that she has hypertensive disease. This patient shows the same response as a normal pregnant patient in her ability to shift large amounts of fluid, sodium, and chloride, without any obvious clinical manifestations. It also shows that after two intravenous injections of sodium chloride, some mechanism came into play by which there was even less disturbance after the third injection in extra- and intracellular fluid and electrolyte than with the two previous.

In the normal subject an excess of water or electrolyte in the plasma, interstitial or intracellular fluid is rapidly excreted by the kidney. The normal pregnant patient has an excess of water and electrolyte in the plasma and interstitial fluid and the pre-eclamptic or eclamptic patient has huge amounts of excess water, sodium, and chloride. If we give test loads of NaCl to such patients, the renal excretion of Na ions increases slightly and temporarily, thus seeming to indicate that the primary abnormal physiology is not in the kidney but in the capillary wall.

When cortisone became available, we gave the drug intramuscularly, and then gave it orally, and when hydrocortisone became available, we gave it intravenously. To date these drugs have been used in amounts up to 400 mg. per day without any obvious improvement in the patient and without any obvious deleterious clinical effects, except that the large injections of hydrocortisone have given us some concern on account of decreases in serum Na and Cl. It is difficult, if not impossible, with ordinary methods of treatment, namely, sodium restriction, mercurial drugs, resins, etc., to produce a normal extra- and intracellular fluid and electrolyte content in pre-eclamptic patients. Since cortisone causes a shift of water and sodium from intracellular to extracellular, where there is some hope of causing its elimination, it may be that this or a similar drug will enable us to cure pre-eclamptic patients without delivery.

We have mentioned the convulsions, coma, etc., associated with water intoxication. There are various reports of patients who were given excessive amounts of water by rectum or intravenously; some died; some became comatose and recovered with appropriate treatment.

Many more studies of dehydration, the opposite of overhydration, hyperhydration, or edema, are available primarily because of the impetus from desert warfare and also because the changes occur earlier and are more dramatic. Adolph and co-workers[1] have contributed much, and they have shown that a 2 per cent loss of water from the normal individual will result in measurable changes in the blood, urine, saliva, pulse, and respiratory rate, etc. This, in a 60 kilogram woman would be equivalent to a loss of 1,200 ml. of water, all of which, according to Adolph, would come from the plasma. Other investigations show that portions would come from the plasma, the extra- and intracellular compartments. Greater losses of water, whether by sweating, diarrhea, or inability to obtain water, are accompanied by changes in the three body compartments with increased changes in the symptoms and signs. Eventually,

the brain is affected, and fever, hyperpyrexia, coma, convulsions, and finally death result. *There is no circulating toxin.* The normal individual is conscious of a 2 per cent loss of his body water, but he is not conscious of a 2 per cent increase because the body from time immemorial has been accustomed to assimilate large amounts of fluid at one time, distributing it to various portions of the body, primarily the muscles of the legs and thighs, until it is either metabolized or eliminated. Adolph and his associates show that as much as 10 L. of water was required to meet the daily requirements of a man working in a temperature of 90° F.

Excess water in the normal individual can be retained at the most for two hours. Repeated intramuscular doses of Pitressin will increase the time interval slightly, but then a diuresis will ensue, and usually more water is lost than was injected.

Wolf[30] stated that the data at hand indicate that man "is more effectively protected against dilution and distortion of the internal environment than against concentration and distortion of the internal environment, and that the regulation of intracellular volume, like that of plasma concentration, may in some cases take precedence over the regulation of extracellular volumes."

The cause of edema in heart failure, acute and chronic glomerulonephritis, pre-eclampsia-eclampsia, and numerous other conditions is still not known. At the turn of the century, edema in these conditions was attributed to an excess of water. About thirty years ago edema was attributed to an excess amount of sodium chloride, and this theory gained support until the last few years, when a number of reports[23] (Squires,[28] Iseri[17, 18, 19]), particularly of patients with heart failure, showed rather conclusively that in these patients large amounts of water, sodium, and chloride were lost. Chloride tended to be excreted in equimolar proportions in sodium. Water was lost from and potassium was taken up into the intracellular compartment of body fluid. The osmotic activity of solutes within the cells appeared to be decreased. The intracellular water and solutes shared in the abnormalities of the body fluid in congestive heart failure, and these intracellular abnormalities consisted of potassium depletion, increased osmolarity of solutes present, and overhydration. The last term, overhydration, is again too much water and a return to the theory of fifty years ago.

We have omitted reference to calcium, magnesium, and bicarbonate, as well as other cations and anions, not because we thought them unimportant, but because their balances would be comparatively small and any changes would be within the limits of error. We believe that similar changes occurred in them with similar significance in organ function.

Summary

Pre-eclampsia-eclampsia is characterized by marked changes in the extra- and especially the intracellular water and electrolyte content. These disturbances are presumably due to a decreased rate of diffusion between the two compartments, the vascular system, and other organs.

Increasing severity of the pre-eclampsia is preceded by greater abnormalities of the intracellular fluid.

Balance studies and weight losses indicate a greater loss of water than of sodium or chloride, suggesting that the interstitial fluids were hypotonic or some of the water was intracellular in origin.

Calculations of the total body water and base balance suggest strongly that a certain amount of base is osmotically inactive, and the amount roughly parallels the degree of weight loss.

A low sodium and potassium diet, diuretics, and other therapeutic procedures have not cured any patients with pre-eclampsia-eclampsia.

The return of the intracellular physiology to normal is aided by a diet low in sodium and potassium (water seems to be ideal) and by delivery.

Methods

A Beckman flame photometer was used for the majority of the Na and K determinations; known standard solutions were used daily. Other blood and urine constituents were determined with accurate methods and the laboratory was frequently checked with unknown blood specimens or solutions. The beam balance weights were taken by residents who were frequently checked. R. P. made the injections for the determinations of serum volume, extracellular fluid, and total body water, and obtained the specimens of blood.

Each patient had her own measured bottle of drinking water and her bottle for urine collection; all were kept in an icebox in the climate room. Measurements of volume were made in the chemical laboratory. The bathroom was locked and used only with a nurse in attendance.

Formulas

W (total water) = Wt. × 0.7
E (extracellular fluid or E.C.F.) = Wt. × 0.2
I (intracellular fluid or I.C.F.) = W − E or W × 0.5
Cl_E (E.C. chlorides) = E × serum chloride
Na_E (E.C. sodium) = E × serum sodium
K_E (E.C. potassium) = E × serum potassium
ΔW (change in total water) is approximately the change in Wt. or W = ΔWt. + (solids out—solids in) + (CHO given + fat burned + 3.2 × urine N)
Fat burned = (insensible Wt. loss − 2.12 CHO − 10.6 × urine N) divided by 3.78.
ΔE (change in E.C.F.) = $E_2 - E_1$ (E_1 is measured or assumed)

$$E_2 = [(E_1 \times \text{serum } Cl_1 + b_{Cl} \text{ (chloride balance)}]/Cl_2$$

ΔI (change in intracellular water) = ΔW − ΔE

$$\Delta Na_E = Na_{E_2} - Na_{E_1} \qquad \Delta K_E = K_{E_2} - K_{E_1}$$

$$Na_{E_2} = Na_2 \times E_2 \qquad K_{E_2} = K_2 \times E_2$$

$\Delta Na_I = b_{Na} - \Delta Na_E$
$\Delta K_I = b_K - \Delta K_E$
Na_I (interacellular Na) = 35 meq./liter × I
K_I (intracellular K) = 115 meq./liter × I
Deficit (or change in osmotically active base) = $\Delta B_I = (W_2B_2 - W_1B_1) - b_{Na+K}$
where B = (serum Na + 10) meq.

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Resident doctors: P. Segal, J. O'Keefe, K. Morimoto, A. Monardo, and J. Dentscheff.

This and many other studies would have been even more difficult without their help.

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Discussion

DR. RUSSELL R. de ALVAREZ, Seattle, Wash.—Anyone who has performed complete metabolic balances is aware of the tremendous amount of effort, thought, precision and calculation, to say nothing of the expense, represented by Dr. Dieckmann's singular contribution today. It is not until one has begun a study of this type, followed the patients carefully for days at a time, practically stood guard like a watch dog over the patient's urine, feces, vomitus, that one understands the frustrations produced by an incontinent diarrheal stool, a dropped or discarded 12-hour collection of urine, or the mysterious appearance of a half eaten bag of salted peanuts on the patient's table. While the terms electrolyte and water balance are, in general, rather loosely used, only careful analysis of data such as those submitted here demonstrates how very rough and approximate are the values obtained in following the electrolyte and water balance in the everyday clinical problems on the ward. Dr. Dieckmann has added another chapter to his long-range study of hemodynamics begun by him over 20 years ago when he reported the increase in plasma volume associated with pregnancy, an observation confirmed by several observers since that time.

The greatest problems in metabolic balance are those relating to complete water balance. The evaluation of complete water metabolism includes the measurement of total body water and of extracellular water and the calculation of intracellular water, as well as the composition of all these spaces. Total body water has generally been stated as comprising 70 per cent of the total body weight. As yet, no unanimous agreement as to the most satisfactory method of determining total body water has been reached. It has been measured by many methods,

including the use of antipyrine, radioactive sodium, and by deuterium oxide. However, it is frequently simply estimated as comprising 70 per cent of the total body weight. I agree with Dr. Dieckmann that this figure is now known to be high in view of the fact that our measurements of total body water, using antipyrine, have approximated 49 per cent to 55 per cent of the total body weight in patients with pregnancy toxemia.

Extracellular water is also measured by various techniques, including the use of chloride, inulin, thiocyanate, and radioisotopes. Of these, inulin space is generally considered to be the most practical. With measurements of plasma sodium concentration and of sodium balance at the beginning and end of such study periods, one determines from the volume change based on chloride study whether sodium has been moved or shifted to or from the extracellular fluid. Where this sodium goes is the debatable issue. This raises some question in my mind as to the propriety of the use of this formula inasmuch as similar circumstances are not necessarily operating at the beginning and at the end of study periods, particularly with the edematous patient who is under treatment.

It would seem that the calculations as presented, on the basis of Elkinton's formulas, were determined on the assumption that the total body water comprises 70 per cent of total body weight. On this basis, too, the concentration of osmotically active base in the body fluids is assumed to equal the concentration of sodium in the extracellular fluid plus 10 meq. per liter; this becomes a significant measure of sodium concentration when clinically applied. In edematous patients, the calculation of total body water at the time when the edema is present is determined by working backward from the time at which the patient was at so-called dry weight.

Once the measurement of the change of volume of total body water has been determined, one should, by having measured extracellular water, be able to determine intracellular fluid volume. The crux of all the determinations, therefore, relates to satisfactory methods of determining total body water. I should like to ask Dr. Dieckmann which method he believes is the most satisfactory.

Dr. Dieckmann states: "According to calculations based on balance studies, a certain amount of sodium is not holding its quota of water." In two of our anuric patients, where the weight remained stable while the serum electrolyte values were progressively decreasing, we, too, felt that a shift of electrolyte from the extracellular phase to the intracellular phase was occurring. It was only by close observation that it was finally determined that fluid was escaping into the peritoneal and pleural spaces. It is conceivable that such extracellular fluid stored in subclinical amounts in what we call "third space" is wrongly considered as a shift of extracellular fluid into the intracellular phase. Unless such third space fluid is obvious, one may be inclined to attribute extracellular electrolyte losses to a shift into intracellular fluid. Possibly the recent work of McIntyre of our Department, in determining differences in action potential, based upon cellular electrolyte content, may provide a solution toward future understanding of this problem.

The recent investigations by Bergstrom and by Francis Moore have shown bone to be one of the principal reservoirs of electrolyte, especially of sodium and potassium. In the light of this newer information, one can only postulate as to whether present methods of complete electrolyte balance may require considerable revision. Shohl has demonstrated that approximately 12 kilograms (⅙ of the body weight) of a 70 kilogram man is skeletal weight. Thus, since Bergstrom has shown that, under the influence of acidosis, adult losses of sodium from bone amount to 54 meq. per kilogram, the skeletal contribution of a 60 kilogram woman would amount to 540 meq., the equivalent of more than 3 L. of extracellular fluid. This would then considerably alter determinations of metabolic balance if this volume of fluid and electrolyte was considered. Even though it is not known whether the administration of sodium and potassium provokes hidden storage in bone, in the absence of depletion of these electrolytes, certainly this possibility would be suggested.

In going over the data in Dieckmann's eclamptic patient, the intracellular sodium concentration seems to be about 37 meq. per liter. This discrepancy between Francis Moore's figure of 47.8 meq., however, might well be explained on the basis of Moore's inclusion of all

sodium, not only that in soft tissue, but that in bone as well. Assuming that enough damage to the cell has been brought about to produce an increased intracellular sodium concentration, it would seem that serum potassium levels should have increased, but this was not apparent from the graphs.

In Dieckmann's eclamptic patient, it seems that only milk was given orally, but it was analyzed for all electrolytes and nitrogen. Another question raised would refer to other avenues of excretion of water and electrolyte. Even though only small amounts of stool would be passed with an intake of milk and other allowable liquids, the component electrolyte and nitrogen excretion in the stool has been found to be highly significant among our patients so studied. Another avenue of escape of high excretion of electrolyte is through the lochia. In one instance our analysis of perineal pads yielded an excretion of as much as 12 meq. of sodium.

It is only by such painstaking methods used by Dr. Dieckmann that a possible solution to the etiology and satisfactory treatment of toxemia of pregnancy may be approached.

DR. DIECKMANN (Closing).—Dr. de Alvarez has commented about possible errors with which we are familiar. We believe our results show a consistent pattern of abnormal extra- and intracellular fluid changes in pre-eclampsia-eclampsia. On the last metabolic day we assumed an intracellular fluid volume of 50 per cent and an extracellular of 20 per cent and calculated backward. We are not relying on any determinations of extracellular or total body water with any reagent; because our values have been inconsistent in these toxemic patients. We are now determining total body water with deuterium and will use a sufficient time for its complete diffusion. We also expect to determine the specific gravity of these patients and thus have a more accurate knowledge of the total body water. We will determine the inulin and Na^{22} spaces.

Our diets contained only minimal amounts of milk, since they were low sodium. There is a certain loss of blood (electrolyte) in the lochia, but in our experience the total amount lost is far less than the values we report. Furthermore, certain patients had total hysterectomies where there was no lochia and their pattern is the same as that of those in whom there was lochia.

Dr. de Alvarez raised the question of a "third space," namely, pleural and ascitic fluid. As long as the patient was undelivered, it is possible that fluid was accumulating in these two cavities. We could detect none in the patients when they were clinically well, but since none died or had a laparotomy in the puerperium, we cannot state that no ascitic fluid was present. In a number of cases the amount of sodium would have been associated with so much ascitic or pleural fluid that I am sure there would have been symptoms and signs. We have repeatedly noted at cesarean section that edematous patients had more than the normal amount of ascitic fluid and occasionally some had evidence of pleural fluid. The electrolyte concentrations in the ascitic fluid always resembled those of the interstitial; the protein concentration tended to be higher than that of the usual ascitic fluid.

The extra- and intracellular changes are difficult to measure. I feel confident, however, that within the next few years the clinician will be treating intracellular changes with as much ease as today he treats pre- and postoperative vascular-renal complications, but with better results. We have been particularly impressed with the need for treating the intracellular changes which occur in patients who have prolonged operations. There will be hemoconcentration, but the interstitial fluid is increased, and there may be slight edema.

We have been careful in all of our studies and there have been no maternal deaths. Our stillbirth and neonatal mortality rate has decreased.

THE ANESTHETIC HAZARDS IN OBSTETRICS*

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THE use of any type of anesthesia is associated with a calculated risk to the patient. With proper selection and administration of the anesthetic agent, this risk is almost negligible, as evidenced by the fact that 18,648 obstetric anesthetics have been administered at the North Carolina Baptist Hospital over a twenty-year period (1935-1954) with no deaths from anesthesia. In an effort to evaluate the factors involved in maternal loss attributed to anesthesia, the following analysis of deaths from anesthesia was undertaken.

Material

Between Aug. 1, 1946, and Dec. 1, 1954, the Committee on Maternal Welfare of the Medical Society of the State of North Carolina reviewed 1,733 maternal deaths of which 45 (2.6 per cent) were, in the opinion of the Committee, primarily the result of anesthesia. Although 913,707 live births were recorded during this period, the exact mortality associated with obstetric anesthesia cannot be determined since large numbers of the patients received no anesthetic agent. In the cases to be reported serious obstetric complications were often present, but in each instance the weight of evidence indicated that the anesthetic agent was the direct cause of death. In the majority of these cases, the responsible mechanism could be established without difficulty (Table I), but in 10 cases (22.2 per cent) this was not possible because of insufficient data. The pertinent information concerning each of these 45 cases is summarized in the following case reports. For brevity, negative findings are omitted.

TABLE I. MECHANISMS RESPONSIBLE FOR MATERNAL DEATHS DUE TO OBSTETRIC ANESTHESIA

MECHANISM	NO. CASES	PER CENT
Aspiration of stomach contents	13	28.9
Spinal shock	11	24.5
Cardiac arrest	7	15.6
Drug reaction	2	4.4
Meningitis	1	2.2
Respiratory paralysis	1	2.2
Indeterminate	10	22.2
Total	45	100.0

Deaths Due to Aspiration of Stomach Contents.—

Case 42.—A 34-year-old white woman, para iii, aspirated vomitus during a low forceps delivery performed at term under open-drop ether anesthesia. She died 5 days later of aspiration pneumonia.

Case 62.—A 36-year-old Negro woman had a blood pressure of 190 systolic, 120 diastolic, in the third month of pregnancy. She had had eclampsia with a previous pregnancy. Therapeutic dilatation and curettage was performed under open-drop ether anesthesia. She vomited during the procedure, and died 72 hours later with consolidation of both lungs.

*Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

Case 124.—An appendectomy and bilateral salpingectomy were performed on a 20-year-old Negro with an ectopic pregnancy and a hemoglobin of 11.0 Gm. She was anesthetized with nitrous oxide, ether, and oxygen, plus 80 units of Intocostrin. Soon after returning to her room, she died as a result of postoperative aspiration.

Case 176.—At 34 weeks' gestation, decompensation occurred in a 29-year-old white woman, para iii, with severe rheumatic heart disease and anemia. Treatment with digitalis and magnesium sulfate resulted in slight improvement. Cesarean section was performed under Pentothal sodium, gas, and oxygen anesthesia. She took the anesthetic poorly, aspirated vomitus on the operating table, and died 24 hours later.

Case 220.—A 25-year-old white woman at term was given open-drop ether anesthesia for delivery after a 27 hour labor. The induction was stormy, and she vomited and became cyanotic on the delivery table. She died 6 hours post partum.

Case 730.—Under Pentothal sodium, ethylene, and oxygen anesthesia, a 32-year-old white woman, para viii, had a tubal ligation two days post partum. Her preoperative blood pressure was 140 systolic, 90 diastolic. Six hours after operation she became dyspneic and cyanotic and coughed tenacious material. Physical examination revealed atelectasis of the right lung, and she died several hours later.

Case 744.—Because of her age, a 45-year-old white primigravida had a cesarean section at term under oxygen and ether anesthesia. The induction was stormy, and vomiting occurred at that time and while the patient was reacting from the anesthetic. She became markedly dyspneic and cyanotic. Bronchoscopy failed to show any obstruction in the larger bronchi, but the patient died after 18 hours.

Case 907.—Under general anesthesia a 26-year-old white woman, para ii, with a blood pressure of 190 systolic, 110 diastolic, had a low forceps delivery at 34 weeks' gestation. Cough, expectoration, and bilateral râles in the chest were noted after delivery. She ran a febrile course, grew progressively worse, and died on the fifth day.

Case 1121.—A 27-year-old Negro primigravida at term was delivered by low forceps under nitrous oxide, ether, and oxygen anesthesia. She vomited and aspirated liquid material while under anesthesia, and died 15 hours later. Aspiration pneumonia and massive pulmonary edema were found at autopsy.

Case 1313.—A 22-year-old Negro, para iii, had a transverse presentation. At term, active labor was followed by sudden cessation of contractions and absence of fetal heart sounds. Five days later, while version and extraction were being performed under ether anesthesia, the patient aspirated vomitus. She died within five hours of shock and respiratory failure. Autopsy was limited to the abdomen and revealed a ruptured uterus with no blood in the peritoneal cavity.

Case 1361.—A 29-year-old white woman, para i, had a blood pressure of 150 systolic, 90 diastolic, and albuminuria 1 plus at term. Heavy sedation and 6 drops of chloroform were used before delivery, which was carried out under pudendal block with 40 c.c. of 1 per cent procaine solution. A few minutes after this solution was administered the patient had two generalized convulsions, associated with vomiting and aspiration of the stomach contents. She died before delivery, and autopsy showed extensive bronchial necrosis resulting from aspiration of gastric contents.

Case 1530.—A low forceps delivery under open-drop ether was performed on a 24-year-old white primigravida at term. At the end of the procedure she suddenly became dyspneic and cyanotic, and death occurred two hours later.

Case 1651.—An 18-year-old white primigravida at 36 weeks' gestation received trichlorethylene analgesia during the administration of 0.5 per cent procaine for a pudendal block. Low forceps delivery was followed immediately by gasping, cyanosis, and death. Autopsy showed massive atelectasis secondary to aspirated food particles.

Deaths Due to Spinal Shock.—

Case 37.—A 21-year-old Negro, para i, at term, was given spinal Pontocaine (exact dosage unknown) plus ether anesthesia for vaginal delivery after a 25 hour labor. She gave a sudden gasp and died before delivery.

Case 48.—A 32-year-old Negro at 32 weeks' gestation was given 17 mg. of Pontocaine by spinal injection, preparatory to an operation for gangrenous appendicitis. She went into profound shock and died suddenly on the operating table.

Case 79.—Prior to cesarean section performed for disproportion, a 24-year-old Negro, para i, with a blood pressure of 180 systolic, 110 diastolic, at term, was given 15 mg. of Pontocaine by spinal injection. She died suddenly two minutes after the subarachnoid injection.

Case 110.—After a 52 hour labor a 20-year-old obese white woman at term was found to have a dead fetus and inadequate pelvic measurements. Her blood pressure was 140 systolic, 95 diastolic. She had gained 50 pounds and had some edema. She was given procaine, 150 mg., for spinal anesthesia preparatory to cesarean section. The patient died suddenly on the operating table before the peritoneum was opened.

Case 148.—A 36-year-old white woman, para ii, became eclamptic at 34 weeks' gestation. Her blood pressure was 180 systolic, 110 diastolic; she had albuminuria 4 plus, and had had five to ten convulsions. After the convulsions were controlled, she was given spinal anesthesia for a cesarean section. The patient died before the incision was made.

Case 242.—Because of disproportion, a 21-year-old white woman, para iii, had a cesarean section at term under spinal anesthesia (10 mg. of Pontocaine). She went into shock during the operation and died on the operating table after the infant was delivered.

Case 395.—Under procaine spinal anesthesia (120 mg.) cesarean section for disproportion was performed on a 30-year-old white woman, para ii, at term. She suddenly became cyanotic, went into shock, and died as the fetus was being delivered.

Case 834.—A 39-year-old Negro, para ii, at term, had a fetus in a breech presentation with relative disproportion. Her blood pressure was 134 systolic, 90 diastolic. Cesarean section was performed under 150 mg. of procaine given for spinal anesthesia. She had a convulsion during the operation and died on the operating table after delivery of the infant.

Case 1146.—At 22 weeks' gestation, a 37-year-old Negro, para iv, had 4 plus albuminuria which had been progressive from the third month. Her blood pressure was 170 systolic, 110 diastolic. She was given a spinal injection of 125 mg. of procaine for therapeutic hysterotomy and tubal ligation, but died immediately after the anesthetic was administered.

Case 1167.—After a 25 hour labor at term, a 30-year-old Negro, para i, was given spinal anesthesia with 15 mg. of Pontocaine prior to cesarean section performed for disproportion. Her blood pressure was 130 systolic, 88 diastolic, before the procedure. Circulatory collapse developed and she died two minutes after the subarachnoid injection.

Case 1413.—A 26-year-old white woman, para i, had a blood pressure of 130 systolic, 70 diastolic, and 1 plus albuminuria at term. After being given spinal anesthesia with 75 mg. of procaine for vaginal delivery, she had a tonic seizure, went into shock, and died 12 minutes after delivery. Autopsy findings were noncontributory.

Deaths Due to Cardiac Arrest.—

Case 1295.—An 18-year-old Negro, para ii, had pre-eclamptic toxemia which was well controlled at term. A normal spontaneous delivery occurred under continuous trichlorethylene anesthesia of five to six minutes' duration. While still under anesthesia the patient became rigid, her heartbeat and respiration ceased, and she died 4 minutes after delivery.

Case 1321.—At 12 weeks' gestation, a 38-year-old Negro, para i, had a blood pressure of 170 systolic, 120 diastolic. She had a history of congestive heart failure in the eighth month of her first pregnancy. Cyclopropane, ether, and oxygen anesthesia was given for a therapeutic dilatation and curettage, but the patient died suddenly before the procedure was started.

Case 1411.—A 36-year-old white woman, para iv, had a missed abortion. Dilatation and curettage was performed under cyclopropane, Pentothal sodium, and oxygen anesthesia. At the end of the procedure the patient became cyanotic and had a pulse rate of 100 and blood pressure of 90 systolic, 50 diastolic. When the pulse ceased, thoracotomy was performed

and the heart was massaged until spontaneous contractions began. After two hours of artificial respiration, spontaneous respirations recurred and continued for three hours. The systolic pressure never rose above 80, however, and the patient died 5 hours after operation.

Case 1494.—Trichlorethylene anesthesia and a pudendal block with 40 c.c. of 1 per cent Metycaine were used for delivery of a 24-year-old white woman, para i, at term. She became cyanotic, her respirations slowed, and no pulse was obtainable. Death occurred after 18 minutes.

Case 1575.—After a spontaneous delivery at term under cyclopropane and oxygen anesthesia, a 28-year-old white woman, para ii, suddenly became cyanotic and died. Autopsy findings were noncontributory.

Case 1594.—Trichlorethylene anesthesia was used for delivery of a 29-year-old woman, para i, at term. She became cyanotic, no pulse was obtainable, and death occurred during delivery. Autopsy findings were noncontributory.

Case 1609.—At 32 weeks' gestation, a 40-year-old Negro, para vi, had 3 plus ankle edema, 2 plus albuminuria, and a blood pressure of 210 systolic, 120 diastolic. The hemoglobin was 9 Gm. Cesarean section was performed under anesthesia with 750 mg. of Pentothal sodium. While the peritoneum was being closed, the pulse became unobtainable. Cardiac massage and intracardiac Adrenalin injection resulted in independent cardiac pulsations after six minutes. The patient never regained consciousness, however, and died 36 hours later.

Deaths Due to Drug Reaction.—

Case 72.—A 32-year-old Negro with a complete placenta previa and minimal blood loss was sectioned at 34 weeks' gestation under local anesthesia with 1 per cent procaine. Large subserosal varices were noted on the uterine wall. The patient had a sudden convulsion and died on the operating table 8 minutes after delivery of the infant.

Case 1600.—A 19-year-old white woman, para i, had rheumatic heart disease with mitral stenosis but no cardiac decompensation. The hemoglobin was 75 per cent. At term, 40 c.c. of a 2 per cent Xylocaine solution was used for pudendal block, during which trichlorethylene was self-administered. Seven minutes after the block was administered, the patient had extensor spasm and a generalized convulsion. The convulsion was followed by shock and death after another 6 minutes.

Death Due to Meningitis.—

Case 60.—Because of disproportion, a 30-year-old white woman, para i, at term, had a cesarean section without labor under spinal anesthesia. Starting on the seventh postpartum day, she had progressive fever and mental depression. Convulsions and nuchal rigidity began on the tenth postpartum day, and lumbar puncture revealed pus. She died after a convulsion on the twelfth postpartum day.

Death Due to Respiratory Paralysis.—

Case 956.—A 20-year-old Negro primigravida had eclampsia, which was brought under good control. Cesarean section was performed at 37 weeks' gestation under cyclopropane and Intocostrin anesthesia. Postoperatively the patient had severe respiratory depression and died within one and a half hours.

Deaths Due to Indeterminate Factors.—

Case 30.—A 40-year-old Negro had an incomplete abortion at six weeks' gestation and was anemic from blood loss. Dilatation and curettage was performed under cyclopropane anesthesia. Her preoperative blood pressure was 110 systolic, 70 diastolic. She died suddenly one hour after operation.

Case 73.—After a long labor, a 28-year-old white woman, para i, had a low forceps home delivery of a stillborn infant under chloroform anesthesia. She died suddenly 20 minutes after delivery, while still anesthetized.

Case 194.—A 35-year-old white primigravida had a history of rheumatic heart disease, but no physical signs of cardiac disease. After 24 hours of labor, she was digitalized

empirically. Low forceps delivery was performed under open-drop ether anesthesia, during which she became cyanotic and hypotensive. She recovered partially, but died one hour after delivery.

Case 283.—A 21-year-old white woman, para i, was given open-drop ether for delivery at term. She suddenly became apneic and cyanotic, and died before delivery. There was no apparent aspiration and no respiratory obstruction was noted.

Case 352.—At 12 weeks' gestation, a 36-year-old white woman, para iii, had an incomplete abortion. The hemoglobin was 65 per cent. Dilatation and curettage was performed under anesthesia with 600 mg. of Pentothal sodium. The patient suddenly became apneic after 8 minutes of anesthesia, and died within 5 minutes.

Case 823.—A 25-year-old white woman, para iii, at term, received chloroform with her contractions for four hours. She suddenly became cyanotic and appeared to be in shock. Chloroform was continued for two hours while she was being taken to a hospital, and low forceps delivery was then performed under ether anesthesia. The symptoms of shock persisted, and she died 3 hours post partum.

Case 1102.—After an 84 hour labor in a 25-year-old Negro at term, the fetus was dead and disproportion was obvious. Vinethene and ether anesthesia was given for cesarean section. The patient became apneic and pulseless, and died as the skin incision was being made.

Case 1114.—A 21-year-old Negro had an incomplete abortion at ten weeks' gestation. The blood pressure was 110 systolic, 70 diastolic, and the hemoglobin was 70 per cent. Dilatation and curettage was performed under 300 mg. of Pentothal sodium. The patient never reacted from the anesthesia and died 2 hours postoperatively.

Case 1582.—A 35-year-old Negro, para xi, had a tubal ligation and appendectomy nine hours post partum. Pentothal sodium (375 mg.), cyclopropane, and oxygen anesthesia was used for the procedure. The patient suddenly became apneic and died 10 minutes postoperatively.

Case 1671.—A 38-year-old white woman, para xii, had a blood pressure of 150 systolic, 90 diastolic, at term. She had been digitalized for cardiac decompensation with her three previous pregnancies, but physical examination at this time showed no evidence of cardiac disease. Following a normal spontaneous delivery under Vinethene anesthesia, the patient died suddenly while still anesthetized.

Major Causes of Death From Anesthesia in Obstetrics

It can be seen from Table I that three major anesthetic complications—aspiration of stomach contents, spinal shock, and cardiac arrest—accounted for 69 per cent of the deaths in this series.

Aspiration of Foreign Material.—

Aspiration of foreign material caused 13 deaths. Nine of these patients received ether; two, Pentothal with gas and oxygen; one, chloroform; and one, trichlorethylene with local pudendal block.

Immediate death from respiratory obstruction followed the aspiration of large food particles in two patients, and in a third patient massive atelectasis produced death in several hours. Nine patients died within two hours to five days after anesthesia as a result of pulmonary edema or pneumonia caused by aspiration of liquid vomitus or small particles of solid food. The obstetric problem probably contributed to the anesthetic complication in the patients with congestive heart failure and severe pre-eclampsia.

Although the recent ingestion of solid food probably was a factor in many of these deaths, faulty administration of the anesthetic appears to be the direct cause of all except one. The delay in emptying of the stomach associated with late pregnancy is further prolonged in labor, and food may be retained in the stomach for 24 to 48 hours. The aspiration of liquid gastric contents is equally dangerous, however.

Aspiration is most common during induction of the anesthesia. Inexperienced anesthetists are likely to attempt to continue the administration of the anesthetic agent, either because they fail to recognize that vomiting has occurred or because they hope to reach the third stage quickly in order to paralyze the vomiting reflex. In the present series this error was probably responsible for most of the deaths from aspiration of stomach contents. Aspiration of vomitus may also occur during recovery from the anesthesia, and it appears that poor postoperative care accounted for one death in this series.

Merrill and Hingson[1] reported the incidence of vomiting during anesthesia at Johns Hopkins Hospital as 6.3 per cent, and estimated that 100 maternal deaths per year in the United States are due to aspiration. In their experience, in the present series, and in Mendelson's report,[2] ether was the anesthetic agent most often associated with fatal aspiration. However, aspiration can occur with any type of anesthesia or with none at all.

Mendelson[2] described two clinical syndromes resulting from the aspiration of stomach contents: (1) respiratory obstruction associated with aspiration of solid particles and producing massive lung collapse with cyanosis and shock, and (2) an asthmatic condition usually associated with the aspiration of liquid vomitus. The latter produces cyanosis, marked tachycardia, tachypnea and dyspnea; wheezes, râles, and rhonchi may be heard over the involved areas of the lung. There is often evidence of congestive heart failure and pulmonary edema occasionally ensues. In patients with respiratory obstruction, chest films show mediastinal shift and consolidation. In those who have aspirated liquids, irregular soft, mottled densities are seen. Infection is an infrequent complication, but is serious when it is associated with either syndrome.

The following precautions should be taken to prevent aspiration during obstetric anesthesia:

1. Withhold food and liquids by mouth after the onset of labor.
2. Avoid inhalation or intravenous anesthetics if the patient has eaten within six hours.
3. Use a transparent anesthetic mask so that vomiting may be immediately recognized.
4. If retching or vomiting occurs, discontinue the induction of anesthesia until the stomach is empty. *Never force anesthesia.*

The delivery room should be equipped with a suction apparatus, a laryngoscope, and endotracheal airways so that treatment may be promptly administered when necessary. The help of a bronchoscopist may be required.

The obstructive syndrome should be treated by putting the patient in the Trendelenburg position, using suction, stimulating the cough reflex, administering oxygen, and, if necessary, performing bronchoscopy.

Asthmatic reactions require treatment for relief of bronchiolar spasm and cardiac embarrassment, as well as suction to clear the airway. Intravenous digitalis, rotating tourniquets, and oxygen administered under positive pressure are indicated for pulmonary edema.

Spinal Shock.—

Spinal shock caused death in 11 cases. Eight of these patients received the dose of the drug that is usually employed for major surgical procedures, and this dose was given without the employment of special precautions or techniques. In all cases death occurred soon after the anesthetic was administered, but in the 6 patients with toxemia of pregnancy it was almost immediate. Seven of the patients were to be delivered by cesarean section, while 2 were being prepared for vaginal delivery.

The physiologic basis for circulatory and respiratory collapse under spinal anesthesia is well established. Dilatation of the peripheral vascular bed results from the blocking of the sympathetic nerves; the consequent reduction in circulating blood volume, venous return, and cardiac output is manifested by a variable degree of hypotension. In severe cases, circulatory collapse occurs and may lead to respiratory collapse as a result of hypoxic depression of the medullary centers. Compensatory mechanisms will usually prevent major reactions when moderate doses of spinal anesthetic agents are used. Severe reactions are common when the dose is excessive or when the level of anesthesia in the spinal cord is too high and affects too great a percentage of the peripheral vascular bed. Respiratory arrest may also result from paralysis of the respiratory muscles by high spinal anesthesia.

Spinal shock is preventable in almost all cases through the use of minimal doses and the "saddle block" technique. Hyperbaric solution should be used to limit the level of anesthesia. The anesthetic agent should not be injected during contractions. The following dosages have been recommended for vaginal delivery: Procaine 35 mg., Nupercaine 1.8 mg., Pontocaine 2.0 mg., and Metycaine 22.5 mg.[3, 4, 5] Roman and Adriani[6] used the following dosages of hyperbaric solutions for 208 cesarean sections: Nupercaine 5.0 to 7.5 mg., Pontocaine 7.5 to 10 mg., and procaine 70 to 100 mg. In 69 per cent of these patients the systolic blood pressure fell below 100. The risk with this dosage range appears excessive and we recommend the lesser values as maximum doses.

Constant vigilance must be maintained when spinal anesthesia is used. Since obstetric patients are unusually sensitive to spinal anesthesia, a mild vasopressor agent should be given to those whose blood pressure values are in the low normal range. If a fall in blood pressure occurs, immediate supportive treatment should be initiated, including elevation of the patient's legs and the administration of oxygen and intravenous vasopressor agents and fluids. Artificial respiration is necessary if respiratory failure develops. The chance of success with the treatment of spinal shock is largely determined by the promptness with which such treatment is instituted. It should be kept in mind that fetal hypoxia is demonstrable in all cases when the maternal systolic pressure is below 80 for five minutes or more, since resting uterine tone will exceed the maternal blood pressure.[7]

Cardiac Arrest.—

Seven deaths resulted from cardiac arrest. Three of these patients had received trichlorethylene and 3 had received cyclopropane alone or in combination with other agents. Pentothal alone was given in one case. Two of the patients had severe toxemia of pregnancy while the others had no serious obstetric complications.

The approximate incidence of cardiac arrest with general anesthesia is 1:5,000.[8] All anesthetic agents can cause cardiac arrhythmias, which Flowers[9] divides into two groups. The first, which is due to increased vagal tone, includes nodal rhythm, delayed A-V conduction time, and bradycardia; these are not considered serious. The second group is made up of arrhythmias which are often fatal: ventricular tachycardia, asystole, and ventricular fibrillation.

Although hypoxia is a common denominator for the development of arrhythmias, associated hypercapnia causes a marked increase in the incidence of cardiac arrest associated with anesthetic agents. Most general anesthetic agents cause some degree of hypoxia or coronary ischemia. Cyclopropane, chloroform, and trichlorethylene increase the irritability of the conductive tissues of the heart and sensitize them to epinephrine. Conversely, ether protects the heart from epinephrine-induced arrhythmias.[10]

Arrhythmias and cardiac arrest occur most frequently in light anesthesia with chloroform, deep anesthesia with cyclopropane, in lower first and second planes with trichlorethylene,[9] and when a poor respiratory exchange causes hypoxia and hypercapnia. Deeper planes of anesthesia depress the myocardium, causing an increase in fatal cardiac irregularities.[11] Excitement stimulates the secretion of epinephrine, to which the cardiac tissue may be sensitized, and predisposes to stormy induction and recovery phases.

Pituitary extract causes a marked constriction of coronary and pulmonary arterioles, bradycardia, cardiac dilatation, and weakening of the beat.[12] The over-all effect is myocardial hypoxia and predisposition to arrhythmias. In both anesthetized and unanesthetized animals, Pituitrin can produce all types of arrhythmias.[13] With cyclopropane anesthesia, these arrhythmias are more often ventricular and thus more serious. Similar effects have not been noted with Pitocin.

Irreversible changes in the vital centers and brain occur within three to four minutes after the circulation stops at normal temperature levels. However, 30 to 50 per cent of the patients who have cardiac arrest may be saved by immediate diagnosis and treatment which requires courageous and immediate action upon the part of the surgeon. Adequate oxygenation of the blood and maintenance of the cerebral circulation are the essential objectives of therapy. Drugs are ineffective, and intracardiac injections are contraindicated until observation of the heart makes it possible to determine the basic lesion which is present.

Disappearance of a palpable pulse and audible blood pressure should be regarded as evidence of circulatory arrest regardless of the anesthetic agent in use. In operative cases the surgeon should check a major vessel in the field to determine whether pulsations are present. If not, he should immediately initiate artificial respiration with 100 per cent oxygen, open the chest through the fourth interspace, and begin cardiac massage by compression at a rate of 80 to 100 per minute. Vigorous and proper massage will produce a palpable radial pulse and a systolic pressure of 80. Life can thus be maintained for long periods until appropriate assistance can be obtained. Hyperventilation should be employed to avoid hypercapnia.

Prophylactic measures include careful induction of anesthesia, with adequate preanesthetic medication when possible, and maintenance of good respiratory exchange with adequate oxygen. Excessive anesthesia should be avoided, and trichlorethylene should never be used for anesthesia. The postanesthetic patient must be closely observed until vital signs are stable, the color is good, and the patient has reacted from the anesthesia.

Minor Causes of Death From Anesthesia in Obstetrics

Drug Reaction.—

Hypersensitivity to local anesthetic agents caused 2 deaths. One of these patients received an excessive dosage, as well as a trichlorethylene supplement, in the presence of known rheumatic heart disease.

Adriani[10] describes two systemic reactions to local anesthetic agents, the first due to idiosyncrasy to the injected drug, the second to overdosage per se. In cases of drug idiosyncrasy, acute collapse follows the use of minute amounts of the particular agent. The patient becomes very pale, respiration fails, and sudden circulatory collapse ensues. Treatment must be immediate, and includes:

1. Artificial respiration through an adequate airway.
2. Restoration of the circulation with intravenous vasoconstrictor drugs.
3. Cardiac massage if asystole is present.

The reaction due to overdosage is characterized by central respiratory and circulatory stimulation, followed by depression and collapse. The patient becomes excited and pale and may have nausea and vomiting, followed by convulsions and then a generalized paralysis. Initial elevation of the respiratory rate, blood pressure, and pulse is followed by apnea, bradycardia, and marked hypotension, sometimes with asystole. Treatment again must be immediate and includes the previously mentioned measures, plus the intravenous administration of a short-acting barbiturate.

The following precautions should be observed to avoid reaction to local anesthetic agents:

1. Use the least amount of drug necessary.
2. Use the weakest solution possible.
3. To prevent intravenous administration, make certain that blood cannot be aspirated through the needle before injecting the drug.
4. Use a short-acting barbiturate for premedication approximately one hour prior to administering the anesthetic agent.
5. Avoid local anesthetic in patients with a history of previous sensitivity.

Meningitis.—

This unusual and frequently fatal complication is an ever present threat in spinal anesthesia. Typically, the first symptoms of meningeal irritation occur between 12 and 24 hours after subarachnoid puncture. Postspinal meningitis is usually caused by bacterial organisms inhabiting the gastrointestinal tract and present on the skin of the buttocks, the commonest of which are *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Aerobacter aerogenes,* and *Alcaligenes faecalis.* Stanley[14] reported that 78 per cent of the cases of meningitis in which *Ps. aeruginosa* was the primary agent followed lumbar puncture or spinal anesthesia. Keefer[15] recently reported 14 cases of meningitis developing after spinal anesthesia for delivery, all of which were caused by gram-negative rods.

The possibility of this complication of spinal anesthesia should be kept in mind constantly, and strict asepsis should be practiced at all times during the procedure. Any fever of unknown etiology in patients who have recently had a spinal tap should arouse one's suspicions. Localizing signs and symptoms should be recognized early, so that immediate specific therapy may be instituted. Early active treatment is essential to avoid fatalities.

Indeterminate Causes.—In 10 cases it was not possible to determine, from the information available, the exact mechanism of death. Seven of these patients received inhalation anesthetics and 3 received Pentothal. The typical story was that of a patient apparently doing well under general anesthesia until she was suddenly found to be cyanotic, pulseless, and without blood pressure. Excessive anesthesia for the procedure undertaken, severe hypoxia, and poor postanesthetic care were probably major factors in these deaths.

Comment

The literature concerning obstetric analgesia and anesthesia is filled largely with enthusiastic reports on the virtues of different agents and methods. Many writers have reported on the use of a given method in a large series of cases. The pharmacologic effects of the agents described are given little attention. Dangers are not emphasized; the management of complications is discussed briefly, if at all; and the report of a maternal death is rare. These publications are submitted with the expectation that the circumstances under which the

method is employed will be the same for the readers as for the author. In the average general hospital, however, personnel available for the administration of anesthesia in the obstetric department is limited. In many small hospitals the attendant must administer the anesthetic himself or direct its administration by an untrained person.

The relative number of mothers who lose their lives as a result of anesthetic complications is increasing, primarily because of the reduction in obstetric deaths from other causes.[16] This fact deserves attention, since deaths from anesthesia, for the most part, result from preventable accidents.

The major factors causing such deaths are poor selection of the anesthetic and errors in its administration. The selection of an anesthetic depends on the condition of the mother and of the fetus, and on the available facilities and personnel.

The present study suggests that the following anesthetics may be contraindicated from the standpoint of *maternal* welfare:

1. Spinal (or caudal) anesthesia in the presence of anemia, toxemia of pregnancy, or hemorrhagic complications of pregnancy.
2. Inhalation or intravenous anesthesia in the presence of respiratory infections or after recent ingestion of food.
3. Trichlorethylene anesthesia under any circumstances.
4. Cyclopropane or chloroform in the presence of known or suspected cardiac disease.
5. Pentothal sodium in the presence of marked anemia.
6. *Any* anesthesia when the maternal condition is poor or inadequately understood.

From the standpoint of *fetal* welfare, general anesthesia is contraindicated whenever fetal hypoxia is present or is anticipated, as in cases of placenta previa, abruptio placentae, prematurity, and maternal diabetes, or when difficult operative obstetric maneuvers are expected. Deep anesthesia, however, is necessary when version is anticipated.

The type and extent of anesthesia used should depend also on the training of the anesthetist and his familiarity with the various agents and apparatuses available. Agents such as curare, if they are used at all in obstetrics, should be administered only by highly skilled personnel, familiar with the possible complications. Spinal anesthesia should not be used when a trained anesthetist is not available. The successful treatment of spinal shock depends on its early recognition, which is obviously impossible without frequent determinations of the blood pressure and pulse. Both the anesthetist and the attendant should be completely familiar with the common complications of anesthesia so that they may be rapidly diagnosed and correctly treated.

In this study, all types of anesthesia except caudal have been associated with maternal death. It should be emphasized, however, that caudal anesthesia is associated with as many grave complications as other anesthetics, and that the same precautions should be used with it as with other agents.

Summary

1. Forty-five obstetric deaths due to anesthesia are reported.

2. The mechanisms responsible for these 45 deaths are discussed.

3. Methods of decreasing the number of deaths from anesthesia in obstetrics are suggested.

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Discussion

DR. RALPH REIS, Chicago, Ill.—Women in labor continue to die from poor anesthesia in North Carolina as unfortunately they do elsewhere. That this is unnecessary is proved by the fact that 18,648 obstetric anesthesias were administered during the past twenty years in Dr. Lock's own institution, The North Carolina Baptist Hospital, without a single death from anesthesia.

Dr. Lock attributes these anesthesia deaths, which he has analyzed so very well, to three factors: (1) poor selection of the anesthesia agent, (2) errors in administration, and (3) the fact that the poorest personnel give the anesthesia in obstetrics in the average hospital. To these I would add the unfortunate demand of most obstetricians that patients be carried down into deep surgical anesthesia for even the most simple obstetric procedures. They forget that light anesthesia is equally satisfactory and infinitely safer for both mother and baby. I become annoyed when an anesthetist apologizes to me because my patient squirms or moves. My retort is invariably a compliment on the lack of deep anesthesia and the hope that this status will continue throughout the delivery which I am conducting.

In considering what Dr. Lock has called "poor selection" we must first take up spinal anesthesia which accounted for over 25 per cent of the deaths—a figure apparently out of all proportion to the frequency of its use. I would decry the continuing use of spinal anesthesia in obstetrics. Almost every worth-while analysis of obstetric anesthesia shows the death rate from routine spinal anesthesia to be higher than that following routine inhalation anesthesia—add to this the continuing frequency of foot drop, bladder and bowel paresis, persistent parathesias, and the price of complete fetal protection from hypoxia seems unwarranted. Furthermore, the continuing stream of articles showing how to reduce the incidence of postspinal headache is eloquent proof of its existence.

One member of this society, who is a real spinal enthusiast, made the following statement in the *Journal of the American Medical Association* last winter: "spinal and caudal anesthesia, if all goes well, are very satisfactory agents." Unfortunately he does not tell us what to do if all does not "go well," how to know when things will not "go well," nor what to do when things have not "gone well." We cannot stop the action of the agent nor can we remove the agent from the spinal canal—reasons enough why we should not use

a method which can be neither stopped nor controlled. Certainly it cannot possibly be compared with inhalation anesthesia which can be stopped instantly by removing the mask or turning off the gas tank.

Three deaths from chloroform in this series are sad evidence that this agent is still being used in spite of all that has been done to prove its lethal qualities these many years. Our newest agent, Trilene, has also been shown to carry potential danger under two conditions —first, when its administration is followed by inhalation anesthesia in a closed system, and, second, when Pituitrin must be used to control hemorrhage. For Trilene increases cardiac irritability and thereby increases the risk of cardiac damage from Pituitrin effect on the coronary vessels.

Last, I would condemn the use of cyclopropane as an anesthetic agent in obstetrics and tell you that it is not used in our birth rooms. Unfortunately, too many have developed a false sense of security concerning cyclopropane because of the ability to maintain a higher oxygen concentration. Forgotten is the fact that cyclopropane is a very toxic agent with a very narrow margin of safety—so narrow that only the expert should be permitted to administer it. In addition cyclopropane passes through the placenta and narcotizes the fetus even though there is an overabundant supply of oxygen present. Most important is the fact that this high maternal oxygen concentration is not reflected in the fetus, in whom the oxygen concentration is low. In addition, it increases uterine tone and is especially unsatisfactory when true uterine relaxation is necessary. Finally, cyclopropane is notorious as a cardiac irritant and is therefore a real factor in the production of "pituitrin shock" and of coronary occlusion. One wonders how many of the 11 "proved" cases of cardiac arrest had coronary spasm or even coronary occlusion and how many occurred which were not fatal immediately.

If spinal anesthesia is bad in obstetrics and chloroform, Trilene, and cyclopropane are dangerous, it appears wise for obstetricians to rely upon one of two courses. The first of these is the use of nitrous oxide, either, and/or ethylene for inhalation anesthesia only when a trained anesthetist is available with suction and laryngoscope at hand and provided the patient's stomach is empty. The only safe alternative is local anesthesia. Unfortunately, the majority are too lazy to use it.

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—My interest in this subject of obstetrical anesthesia has been increased by this fine paper of Dr. Lock's and has stimulated me to make a spot survey of this problem in the State of Maryland. I wished to ascertain the incidence of deaths during delivery and also to try and evaluate what type of anesthesia is most suitable and gives the lowest rate of mortality. Through the aid of the Maryland State Health Department and a number of my colleagues I have collected the following data.

A survey of the various counties of Maryland, for a period of 17 years, showed 473,890 deliveries with a death incidence of 11, attributable to anesthesia; 10 of these were due to inhalation anesthesia (2 reports note aspiration of vomitus) and the one remaining was due to caudal anesthesia. In the City of Baltimore during a fourteen-year period, there were 267,273 births. In this group there were 31 fatalities attributed to anesthesia. A breakdown of this group runs about parallel to others surveyed. Twenty-two deaths were attributable to the inhalation type of anesthesia, the remaining were of the induction type, i.e., spinal 3, saddle block 1, caudal 2, local 1, paravertebral and pudendal block 1 each. The disparity between the death incidence in the county, 11 in number, and the incidence of 31 occurring in the city, is due to the fact that a number of the seriously ill county patients were transferred to the city and there was a failure to assign the deaths to their resident county.

A survey was then made of obstetrical anesthesia in 4 hospitals in the City of Baltimore. The analytical data of the obstetrical anesthesias at the University Hospital parallels the findings noted in the other institutions. The University's survey extends over a five-year period, 14,900 patients being delivered. Total anesthetics 12,054. There was 1 death in a nullipara with spinal anesthesia; 10 mg. of Pontocaine in 10 per cent glucose and 25 mg. ephedrine were given. Dr. Robert Dodds, Chief of the Department of Anesthesia, is of

the opinion that this death was unfortunately due to overdosage and that 5 mg. of Pontocaine is the proper dosage. Postmortem examination showed no gross abnormality, whereas the microscopic examination showed petechial cerebral hemorrhages. No other deaths occurred.

Eighteen types of anesthesia, and combinations of methods, were used:

Local, with inhalation
Saddle block
Continuous spinal
Continuous caudal and intravenous
Intravenous alone
Intravenous with inhalation
Epidural
No anesthesia
Local alone
Saddle block with inhalation
Caudal
Epidural
Spinal continuous alone
Spinal continuous with intravenous
Spinal continuous with inhalation
Spinal single shot
Spinal single shot with intravenous
Spinal single shot with inhalation.

Of the total number of anesthesias given, 12,048, the saddle block type was administered in 9,176; no deaths or paralysis occurred. In the other hospitals surveyed it was found that the saddle block type of anesthesia was the procedure of choice.

The report from St. Agnes Hospital, covering a five-year period, and reported by Dr. J. King B. E. Seegar, Jr., shows there were 5,250 patients in whom saddle block was administered and there were no deaths or paralysis.

The report from Mercy Hospital covering a seven-year period, and reported by Dr. Frank Morris, shows 12,201 saddle block anesthesias were given with no death or paralysis.

The report from the Hospital for the Women of Maryland presented 1,298 patients receiving induction anesthesia; this was 86.5 per cent of the total and there were no deaths or paralysis. This makes a total of 27,925 who received saddle block anesthesia with no paralysis and no deaths.

With inhalation anesthesia the high rate of mortality is frequently due to aspiration of the stomach contents. As we know, in the latter stages of pregnancy atony of the stomach may last for many hours with retention of ingested food. We feel that this atony may be a part of a general systemic loss of muscular tone. This has been observed in the urinary tract during normal pregnancy. In the last trimester there is complete loss of peristaltic activity of the ureters and the tract becomes an inert sac. We have produced this same phenomena experimentally as follows: a group of normal, nonpregnant women were given large doses of progestogenic substance hypodermically over a period of nine weeks; the ureteral activity was observed weekly by the use of Trattner's hydrophorograph. After the prolonged priming the ureter showed no peristaltic activity, was just an inert sac. We are now starting a similar group of experiments on the muscular behavior of the stomach in a group of pregnant and nonpregnant women. These women will be primed with large doses of progestogenic substance and weekly tracings of the gastric peristalsis will be recorded. The technique consists of swallowing a thin-walled rubber bag which is distended with fluid and connected to a kymograph drum. Fluoroscopic studies of the emptying time will also be made. It may be possible to overcome the atony with large doses of estrogenic substance. Our results will be published at a later date. Since aspiration of vomitus is one of the most frequent causes of death during delivery, more emphasis should be placed on the danger of eating just prior to onset of labor. If this occurs within four hours of active labor, gastric lavage should be instituted.

With induction anesthesia one of the greatest causes of disaster is overdosage. Our Department of Anesthesiology recommends for spinals a dosage range of 5 to 8 mg. of Pontocaine when a cesarean section is performed; for vaginal delivery the obstetrical department uses a saddle block of 2.5 mg. (1 c.c.) of Heavy Nupercaine. Another precaution is that spinal needles should never be cleansed with detergents and also that spinal headaches will be greatly diminished with the use of a small-caliber spinal needle. It is also worthy of mention that the probability of arachnoiditis developing is greatly diminished if the spinal ampules are autoclaved instead of being soaked in an antiseptic solution for the glass ampule may crack and the fluid be contaminated.

The deaths occurring in the counties and associated with anesthesia were 11 in number, all due to inhalation anesthesia except one which was due to caudal anesthesia.

In a summary of the deaths associated with anesthesia, occurring in the city, we find 31 fatalities. Inhalation anesthesia was used in 22 cases; of the remaining, spinal anesthesia was used in 3, caudal in 2, local in one, paravertebral and pudendal in one each, and one was due to saddle block.

In the hospital group comprising a total of 27,925 patients who received saddle block anesthesia, there were no deaths and no paralysis.

Conclusion.—To diminish effectively the high mortality rate due to anesthesia at delivery the ideal is to have a fully competent anesthetist present. This is difficult to accomplish and will depend in a large measure on more intensive student teaching in this subject. Until this ideal can be attained a procedure which is easily taught and has a low mortality rate should be adopted. That method in our experience is saddle block anesthesia, the merits of this procedure having been well attested by the recorded data.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—In view of the increasing use of trichlorethylene for analgesia in the United States, supplemented by pudendal block, it seems important to clarify the implications of Dr. Lock's paper in relation to the safety of trichlorethylene when given and especially when supplemented by agents which include Adrenalin and/or Pitressin. In order to clarify this situation I should like to ask Dr. Lock a few questions which no doubt are answered in his complete paper.

His series, as I understand it, includes one case of self-administered trichlorethylene supplemented by pudendal block, and, the anesthetic agent being procaine, I assume Adrenalin was given. I believe the implication is that death was due to the analgesic action of trichlorethylene, Adrenalin, and/or Pitressin. I should like to ask him if he feels definitely that this sequence of events is the explanation for that death and whether there were any other possible explanations? Was the trichlorethylene definitely self-administered or did somebody lay a hand on the mask and augment the degree of anesthesia? Does he know of other deaths following self-administered trichlorethylene in which Adrenalin and/or Pitressin played a role?

If Adrenalin is at fault, this can be avoided by the use of Xylothene which does not require Adrenalin.

It seems to me that, in view of the widespread and increasing use of trichlorethylene throughout the country, we should explain these questions. If trichlorethylene not associated with Adrenalin and/or Pitressin is dangerous, that fact should be publicized. I know of several clinics which can report 4,000 to 5,000 cases in which trichlorethylene was used and supplemented by procaine and Adrenalin without mishap. While I am very much impressed by this single death—and I take it that it is the only death in the series after self-administered trichlorethylene—I am not yet and without further evidence prepared to say that trichlorethylene self-administered for analgesia is not a relatively safe analgesic agent.

DR. HAROLD C. MACK, Detroit, Mich.—I wish to present some data from Michigan which support Dr. Lock's evidence of the anesthetic factor in maternal mortality. I am indebted to Drs. Harold Ott and Harold Longyear for statistics gathered by the Maternal Mortality Committees of Detroit and Michigan.

In Detroit during the five-year period of 1948-1952, 12, or 5.8 per cent, of 255 maternal deaths were attributed to anesthesia. The Committee judged that 83.4 per cent were preventable. Of these deaths, 6 followed spinal anesthesia, 5 were attributed to inhalation anesthesia, and one to caudal. Published figures for the State of Michigan gave 22 fatalities from anesthesia, an incidence of 8.4 per cent. All methods of anesthesia, including local infiltration, were represented among the deaths ascribed to anesthesia.

Studies such as these point out the importance of careful individual investigations of all maternal deaths. In many instances it was shown that deaths associated with toxemia, hemorrhage, or vascular disease complicating pregnancy were in reality due to the effects of poorly chosen or improperly administered anesthetic agents. In 4 deaths of the Michigan survey attributed to spinal anesthesia this method was used to manage toxemia of pregnancy. It is probable that the anesthetic risk, even though formerly unrecognized, has always played a large part in maternal and fetal fatalities ascribed to other obstetric complications.

Prevention of toxemia and of many of the causes for infection and hemorrhage is still not possible. Deaths from anesthesia, however, are largely preventable and their elimination is perhaps one of the most direct attacks which can be made upon maternal mortality.

DR. LOCK (Closing).—I want especially to answer Dr. Eastman's question. The patient who died following self-administered trichlorethylene analgesia did not receive Adrenalin or Pituitrin but did receive 40 c.c. of 2 per cent Xylocaine. That is a gross overdosage, and we thought death was due to that agent rather than to the trichlorethylene. The death was characteristic of an overdosage reaction to local anesthesia.

I wish to make one other comment: In the philosophy of our committee we cannot accept that any death from anesthesia is really nonpreventable. There has been abuse of anesthesia in obstetrics. I agree with Dr. Eastman and Dr. Reis' belief that there are very few obstetric procedures which require anesthesia of any significant degree.

AN EXPERIMENTAL PROGRAM WITH COLPOSCOPY*

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WE WISH to report our experience with colposcopy as observed for a year and a half. We were persuaded to initiate the study by Dr. Karl A. Bolten who came to our institution by invitation from Bonn, Germany, as a Teaching Fellow in the Department of Obstetrics and Gynecology. The type of colposcope presently used by Hinselmann, and greatly improved over the one he used in his pioneer work thirty years ago, was secured through the generosity of the Cancer League of Philadelphia, a group of women dedicated to cancer control in all its aspects. Our associates, Dr. Warren R. Lang, an Assistant Professor in the Department, and Dr. Gabriel Tatarian, a Resident, soon became enthusiastic about the positive value of the method in studying the abnormal cervix as an aid in diagnosing cervical cancer. As we became increasingly interested in the preliminary work, it seemed that colposcopy had even more to offer than the objectives mentioned, for we were tremendously impressed with the educational advantages of the instrument. Seeing the cervix under magnification of ten to twenty times relays visual impressions of a normal and abnormal surface that actually remain photographed in memory. This has meant an entirely different concept of the cervix as it is inspected ordinarily, for one instinctively recollects the possible relationship and details that magnification has stressed. Added to this phase are the excellent color photographs made possible, for they have added much to the visual education of students, house, and attending staff. We have approached this study with no preconceived ideas as to its ultimate value to ourselves and others.

After several months of preparatory study, in both clinic and library, an experimental program was begun. Primarily, colposcopy and color photography were emphasized to gain skill; gradually correlation with cytologic and histologic findings was established, and finally an individual record card system was set up for a consecutive study. All in all, approximately 450 colposcopic examinations have been made. It is on these premises that the remainder of the presentation is based and complete credit for the study belongs to Dr. Lang with the assistance of Dr. Tatarian. Dr. Bolten was associated with us during the first six months of the program.

As stated, Hinselmann[1] published the first paper on colposcopy thirty years ago. Since then the method has been used successfully as a cancer case-finding method in various countries of the European and South American con-

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tinents. Although the method antedates the widespread interest in the cytologic smear by almost two decades, it has been used only sporadically in the United States. We have speculated a good deal about this in view of the contemporary and intense interest in the development and detection of early cervical malignancy.

In this country Martzloff[2-6] and Emil Ries[7] have reported extensive experience with the instrument; others have written of the fundamentals of the method (Duncan,[8] Peightal,[9] Farrar,[10] Emmert,[11] Steffen[12]) the paper of Norris[13] being the most comprehensive review. Diverse modifications and simplifications were proposed by Gellhorn,[14] Maryan,[15] Lifvendahl,[16] and Sacks,[17] to whose articles the reader is referred for further details. A brief but incomplete review of the method has been given in English by Hinselmann[18] and his recent monograph[19] has just been translated from the German. A translation of Wespi's[20] book is also available. Various summaries of foreign colposcopic experiences have appeared in English in the abstract journals and we[21, 22] have recently reported upon our own experience and impressions. Whether North American disinterest in colposcopy has stemmed from a previous lack of satisfactory, inexpensive color film, as Ries believed, or from the decreased flow of continental medical literature, especially from Germany, preceding and during World War II, or whether the method itself has seemed to be of little worth is difficult to state. Perhaps association with a complete system of unfamiliar histologic terminology has discouraged its acceptance. In any event, there is evidence of resurgent curiosity about colposcopy at the present time.

Principles of Colposcopy

The principle of colposcopy is simple. It consists of stereoscopic visualization of the cervix under magnification with direct lighting. It depends upon the fact that changes in the cells and cellular architecture of the surface epithelium are detectable with surface enlargement. The colposcope we use, made by J. D. Moeller Company, Hamburg/Wedel, Germany, and identical with the one used by Hinselmann today, magnifies ten and twenty times. It should be realized that with such magnification an area 1 mm.^{2} in actuality, appears 1 cm.^{2} when magnified ten times and 4 cm.^{2} when magnified 20 times.

The colposcope is a binocular instrument mounted on an adjustable stand with a transformer in the base. By means of a side lever, magnification can be changed from ten to twenty times without refocusing. When correctly placed, the colposcope "looks" at right angles upon the surface of the cervix previously exposed by a speculum. The distance from the terminal lens to the cervix is approximately 20 to 22 cm. and the colposcope does not enter the vagina. A green filter is attached and can be utilized as desired to increase contrast, especially of blood vessels. Our own particular colposcope has a built-in Leica attachment for taking 35 mm. Kodachrome pictures. This is an excellent method of securing a permanent record of normal and abnormal findings.

Our method of procedure is outlined in Table I. We first insert the speculum with the patient in the usual lithotomy position and then adjust the colposcope. The cervix is first viewed in situ; then, after gentle cleansing; and, next, after the application of 3 per cent aqueous solution of acetic acid better to delineate detail. Last, aqueous iodine (Schiller test[23]) is applied. We examine as much of the cervical canal as possible and sometimes even the vulva and vagina as well.

We have had no personal experience with ultraviolet colposcopy[19] or with the colpomicroscope of Antoine and Grünberger.[24] Their instrument magnifies 160 or 200 times. It seems to us that such great magnification defeats the purpose of the colposcopy—namely, a close, yet rapid scanning of the cervical epithelium.

TABLE I. TECHNIQUE OF COLPOSCOPY

1. Insertion of speculum
2. Adjustment of colposcope
3. Inspection of cervix
a. As is, in situ
b. After gentle cleansing
c. After application of 3 per cent acetic acid
d. After aqueous iodine (Schiller test)
e. Change in magnification, green filter as desired

Colposcopic Findings

In a previous publication we[21] have reviewed the various findings, both normal and abnormal, that are noted by the colposcopic method. As might be expected, colposcopic technique, concepts, and nomenclature have already been established. These are mainly the product of Hinselmann's interpretations, subject to some differences of opinion by others.

There are three normal findings:

1. *Squamous epithelium* appears as reddish pink with fine white dots.

2. *Columnar epithelium* has a bubbly or grapelike appearance *(Träubchenbildung)*. It normally lines the endocervix but may occur ectopically on the portio adjacent to the anatomic external os. This is what has been termed *ectopy (ectopie)* by Hinselmann, and heteroplastic endocervical tissue by Mohler.[25]

3. The *transformation* or *transition* zone *(Umwandlungzone)* is a normal finding not sufficiently appreciated by those unfamiliar with the colposcope. It consists of a mixture or intermingling of both squamous and columnar epithelium and presumably represents the interplay of squamous epithelium as it grows back toward the os to replace columnar epithelium (Fig. 1). In such instances one sees ectopic islands of columnar nature in squamous epithelium, Nabothian cysts, gland openings, and areas of vascularization. This situation is the usual colposcopic finding that the clinician may call "eversion," "erosion," "ectropion," "chronic cervicitis," or "cystic degeneration."

When the epithelium becomes abnormal, whether benign or malignant in nature, the colposcopic findings vary correspondingly. It is by these various changes noted colposcopically that carcinoma may be suspected. A listing of the significant findings is given in Table II.

TABLE II. COLPOSCOPIC FINDINGS OF ABNORMAL EPITHELIUM INCLUDING EARLY CERVICAL CANCER

1. True leukoplakia
2. Ground leukoplakia
3. Mosaic leukoplakia
4. Abnormal transformation zone
5. True erosion
6. Uncharacteristic red areas
7. Yellowish areas of proliferation
8. Adaptive vascular hypertrophy
9. Iodine-negative areas

True *leukoplakia* is often found in or near an early carcinoma. Colposcopically, the term refers merely to a whitish patch, the area being white because

of cornification, or parakeratosis histologically.[20] The vascularity of the underlying connective tissue is therefore less noticeable on inspection of the surface. On occasion, true leukoplakia is noted grossly but there are two specific forms of colposcopic leukoplakia that are discernible only by magnification. They are *mosaic* leukoplakia *(Felderung),* which term is descriptive of its pattern, and *ground* leukoplakia *(Leukoplakiegrund),* which consists of a whitish-yellow patchiness with diffuse red dots. The histologic explanation of the colposcopic appearance of mosaic and ground is diagramed in Fig. 2. From the beginning of his studies Hinselmann[26] has stated that leukoplakia in its several forms may be a facultative but not necessarily an obligatory step on the road to carcinoma. In this viewpoint he states that he has often been misquoted. Limburg[27] states that about 10 per cent of cases of the various forms of leukoplakia are associated with preinvasive or invasive carcinoma.

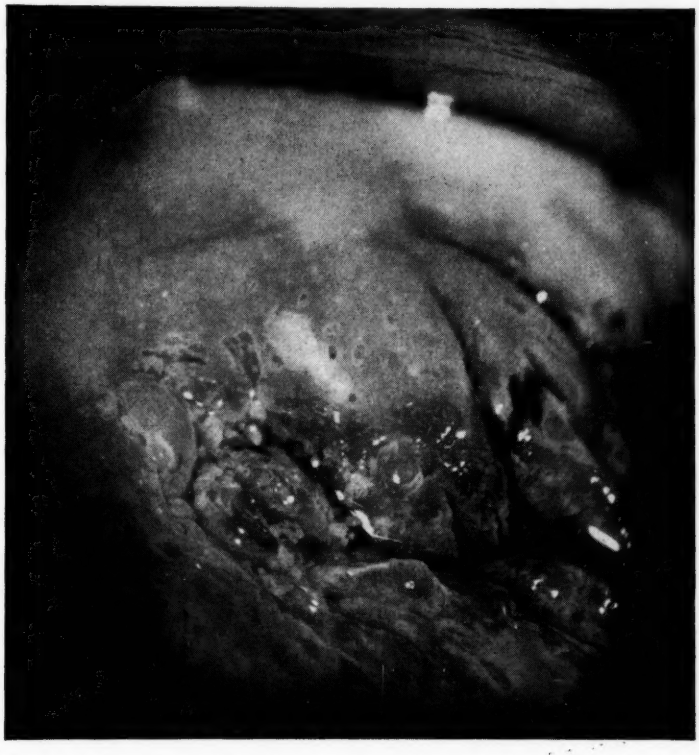

Fig. 1.—Picture of a transformation zone. This shows the right end of a transverse cervical os of a woman two months after a spontaneous abortion. Note the irregular formation of columnar epithelium at the external os, the islands of ectopic columnar epithelium, and the gland openings.

Irregular blood-vessel formation with corkscrew arrangement, so-called adaptive vascular hypertrophy, may also be present. This is not surprising when one considers the disordered architecture that accompanies new growth. Areas of true erosion with heavy vascularization may also be seen, just as ulceration often characterizes gross carcinoma. Glassy, yellowish, necrotic-appearing proliferative areas are sometimes visualized. These represent an exophytic growth in miniature. At times there may be only red areas of vascularization *(rote Fläche)* or abnormal transformation zones with heavy leukoplakic rims around the gland openings and with increased vascularity. In some instances the only positive colposcopic feature is a "silent" iodine-nega-

tive area. Hinselmann believes that when an area of atypism or early carcinoma is visualized by the colposcope, abnormal histologic findings are almost invariably seen. On the other hand, one would expect few or no colposcopic findings or, in fact, cytologic changes, in so-called "spray carcinoma" (Schiller,[28] Hueck[29]) in which the carcinomatous transformation is limited to the basal zone of the epithelium and which invades rapidly while the external surface remains unchanged.

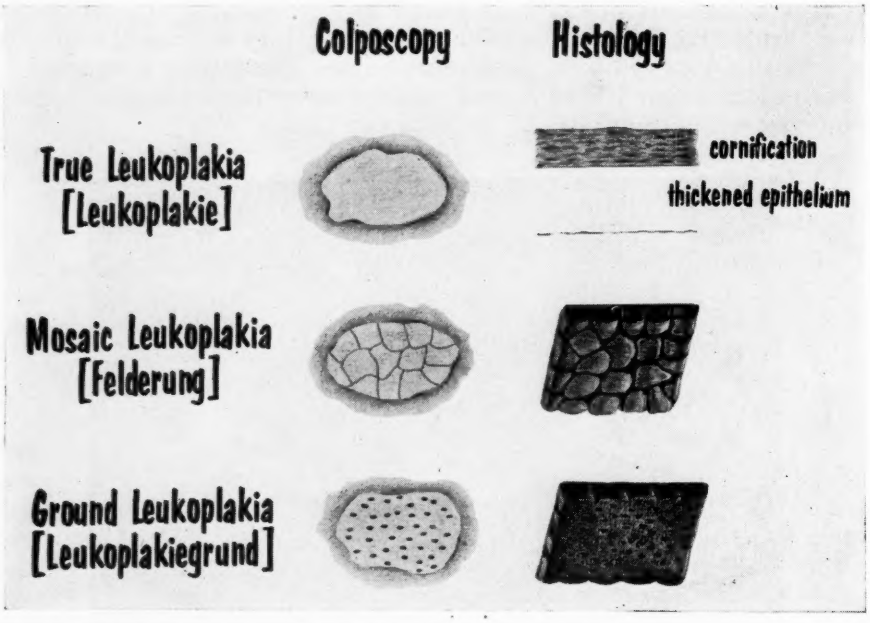

Fig. 2.—Histologic explanation of the various forms of leukoplakia as seen by the colposcope. With true leukoplakia there is a layer of cornification on the surface; only biopsy can tell whether the epithelium beneath is normal. Mosaic and ground leukoplakia indicate abnormal types of epithelial architecture, both appearing as yellow-white areas, the former with a mosaic pattern of reddish lines, the latter peppered with reddish spots. The redness is the result of thinning of the epithelium with connective tissue showing through. A form of mosaic leukoplakia may also result from closely set gland openings with thickened leukoplakic rims (not diagramed). The diagrams of the histologic architecture of mosaic and ground leukoplakia are three dimensional as seen from the under surface of the epithelium (modified from Wespi).

These findings as suggestive of early cancer have been well documented in the literature by both Hinselmann and later investigators. After studying 91 cases of Stage 0 and 25 cases of early Stage I, Morari and Strametz[30] state that the colposcopic findings of Stage 0 and early Stage I are about the same and that there is no specific or infallible colposcopic finding to indicate malignancy or the presence or absence of invasion. Some form of leukoplakia was found in about half of these early cases. This agrees with the findings of others (Kodolitsch,[31] Vöge,[32] Mestwerdt[33]). In surface carcinoma, according to Wespi,[20] the most frequent finding was slightly elevated yellowish-red or whitish epithelium with large loops of capillaries. Limburg[27] classifies the colposcopic findings of early cervical malignancy into five groups: (1) leukoplakia, (2) mosaic leukoplakia, (3) ground leukoplakia, (4) true erosion with loss of surface epithelium, (5) abnormal transformation zones (including thickly rimmed gland openings, yellow proliferative areas, and adaptive vessel hypertrophy). In his experience he interprets these various manifestations percentage-wise as indicative of preinvasive or invasive cancer in 9.4, 13.2, 9.9, 9.9, and 9.8 per cent, respectively.

Personal Experience With Colposcopy

In our introduction we related briefly the premises and evolution of this experimental program with colposcopy, involving some 450 examinations. Primarily we needed to become familiar with the so-called normal cervix. Soon thereafter work began with patients referred from the gynecologic and obstetric clinics because of clinical abnormalities or an unusual cytologic report. These earlier observations were disciplinary in nature, and not systematically recorded until it was thought that acceptable accuracy of observation had been attained.

Accordingly our impressions and opinions are based on recorded information and some color photography incident to 168 patients studied consecutively during the past year. The aim has been to catalogue the history, gross appearance, colposcopic findings, cytologic smear,* and biopsy reports of as many of these patients as possible or available. A screening program has not been attempted—first, because of the time element involved in self-education; second, because the positive value of the method in screening has already been proved by experienced colposcopists during the past thirty years.[34-37]

Of our recorded patients, 15 had obvious squamous-cell carcinoma (one a possible adenoacanthoma) (Stage I, 5; Stage II, 3; Stages III and IV, 7). Of 7 recurrent or unarrested cases seen, 3 had been primarily designated as Stage 0. Abnormal findings were present in 23 patients, all the lesions being benign histologically. The remaining 123 patients of the 168 total had benign findings throughout. The detailed study follows.

Our experience with early cervical malignancy seen before treatment is a continuation of work previously reported. Once again we[21] state honestly that colposcopy has not primarily diagnosed a single malignancy. It did, however, delineate more clearly the need of study in several patients. Although we have examined all stages of cervical malignancy colposcopically we have presented only Stages I and II in chart form (Tables III and IV).

Carcinoma in situ is a rare histologic diagnosis in our institution[38] but we have studied 3 previously treated ones. One was a suspicious or recurrent lesion with suggestive cytology in an obese woman previously treated with local radium that revealed corkscrew vessels in a thin glassy epithelium with evidence of ground leukoplakia. Subsequent death from acute coronary occlusion resulted in an autopsy finding of invasive cancer. The other 2 had been managed by circular cervical biopsy previously, were symptom free, and colposcopy and cytology were within normal limits. Repeat circular biopsy was negative in one and eventually a total hysterectomy disclosed no evidence of cancer. In the third, repeat biopsy is again to be done for academic reasons.

We have studied 5 cases of Stage I, each of which showed several of the expected colposcopic findings. Interestingly enough, each case showed some variety of leukoplakia; 2 showed only true leukoplakia; 2 showed the three types, and one ground only. In one of these (F. G.) we were able to determine the exact site of biopsy of colposcopy which disclosed a localized proliferative area, while in another (O. H.) a suspicious smear was obtained from an area of pronounced leukoplakia; the remainder of the cervix yielded a doubtful smear only. This is contrary to the opinion of Limburg,[39] who states that a smear from an area of true leukoplakia would be more likely to be negative since it may completely cover an area of frank carcinoma. The colpophotograph on one case (I. M.) is shown in Fig. 3.

*Cytologic results in our institution are reported as "negative," "doubtful," "suspicious," and "positive." Since we do not believe the smear is fully diagnostic of malignancy, very few smears are classified as "positive."

TABLE III. STAGE I CARCINOMA OF CERVIX

NAME	AGE	RACE	GRAVIDITY, PARITY	SYMPTOMS	CERVICAL FINDINGS	STAGE	CYTOLOGY	COLPOSCOPY	BIOPSY
F. G.	58	White	iii/iii	Postmenopausal yellow discharge three months	Lacerated, red "erosion" posterior lip, friability	I (early)	Doubtful	Inflammatory transformation zone, especially posterior lip. Leukoplakia. Elevated "island" with corkscrew vessels at 7 o'clock	Squamous-cell carcinoma
M. H.	51	Negro	xii/x	Postmenopausal spotting four months	Atrophic cervix, friable	I	Suspicious	Inflammatory transformation zone. Ground leukoplakia. Elevated islands of corkscrew vessels	Squamous-cell carcinoma
I. M.	42	Negro	0/0	None	Red "erosion"	I	Doubtful	Mosaic and ground leukoplakia, red areas	Squamous-cell carcinoma
S. B.	30	Negro	i/i	Menorrhagia, metrorrhagia, for one month	Laceration, red "erosion"	I	Suspicious	Leukoplakia, true erosion, yellow raised areas	Squamous-cell carcinoma
O. H.	31	White	v/v	Postcoital spotting one year	Red "erosion." Gross leukoplakia at 9 o'clock	I	Suspicious	Inflammatory transformation zone with marked leukoplakia	Squamous-cell carcinoma

TABLE IV. STAGE II CARCINOMA OF CERVIX

NAME	AGE	RACE	GRAVIDITY, PARITY	SYMPTOMS	CERVICAL FINDINGS	STAGE	CYTOLOGY	COLPOSCOPY	BIOPSY
E. L.	53	White	iii/iii	Bleeding seven years after menopause	Hyperemia, central "erosion"	II	Suspicious	Yellow proliferative areas with abnormal vessels, small ulceration, all extending into canal	Squamous-cell carcinoma
I. P.	78	White	i/i	Bleeding 28 years after menopause	Friability, exophytic growth	II	Suspicious	Large yellow proliferative area with abnormal vessels. Some leukoplakia	Squamous-cell carcinoma
E. L.	34	Negro	v/v	Postcoital spotting two months	Grossly carcinoma	II	Suspicious	Large yellow proliferative area with abnormal blood vessels	Squamous-cell carcinoma

The three Stage II cases were characterized by proliferation with abnormal blood-vessel formation. One also showed true leukoplakia. Seven Stage III and IV patients showed similar findings in addition to ulceration readily visible grossly, but are mentioned for completeness in the study of all stages of cervical cancer.

Four patients with early recurrence of invasive cancer following irradiation therapy were studied. Both colposcopic and cytologic findings were suggestive and biopsy proved positive. There is little in the literature regarding colposcopy in this regard. The method might help to find abnormal areas in the presence of suspicious cytology without gross findings.

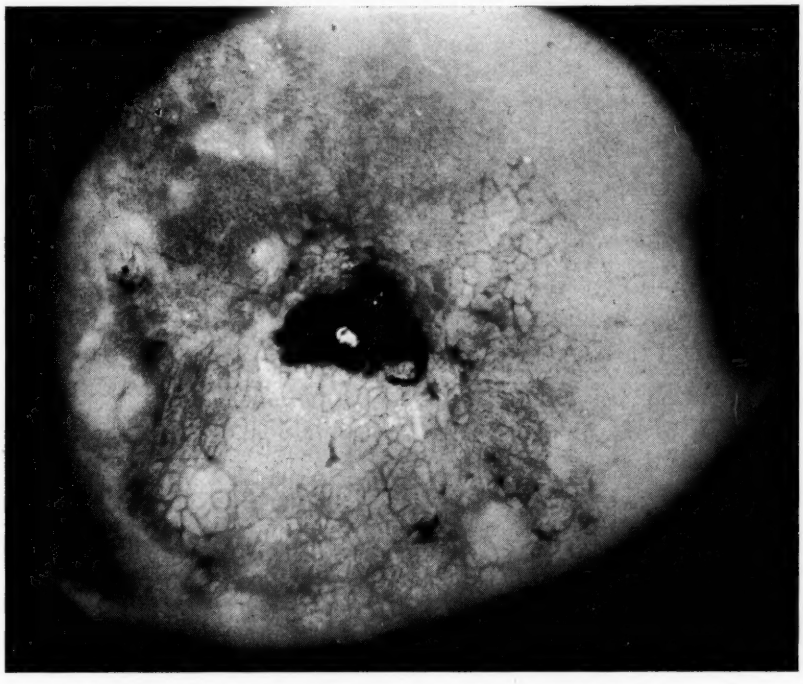

Fig. 3.—Early Stage I cervical carcinoma (Patient I. M.) as seen by the colposcope. Note mosaic leukoplakia, easily detected at 2 and 7 o'clock and ground leukoplakia inferior to true leukoplakia at 11 o'clock. The slightly elevated area slightly lateral to and below the area of ground leukoplakia showed adaptive vascular hypertrophy.

The group of 23 patients with atypical findings—true leukoplakia, mosaic and ground forms or an inflammatory transformation zone—have proved most interesting in follow-up. The colposcopic changes were rarely sufficient even to suggest malignancy. In 6 of them cytology was doubtful or suspicious. Biopsies of different types have shown varying degrees of atypism. One, with marked mosaic leukoplakia and a suspicious cytologic smear in addition, has not yet been biopsied because of slowly subsiding pelvic inflammatory disease. The latter in itself may well be a factor in the suspicious smear.[40]

Benign colposcopic findings were recorded in 123 patients, routine cytologic smears being negative in 101 of them. If the portio does not reveal intact squamous epithelium, however, it is our belief, as we have frequently emphasized, that the cervix should be restored to a normal state by appropriate treatment, either by electrocauterization or by surgical means.[41]

Comment

Colposcopy will never replace the fundamental means of diagnosing cervical cancer, viz., history, pelvic examination, cytologic smear, biopsy, and fractional curettage. Although the appearance of symptoms cannot always be correlated with the onset of carcinoma, it is true that an abnormal pattern of bleeding is nearly always the first indication, not only of an invasive lesion but of an intraepithelial one as well.[42] Prompt pelvic examination in the presence of symptoms is mandatory; routine periodic pelvic examination for all is the ideal goal to be achieved. In general how does colposcopy compare with cytology in efficiency and usefulness? If both methods are available it is not a problem of colposcopy *versus* cytology but instead a complementary one of colposcopy *and* cytology. Besserer,[43] Berger,[44] Held,[45] and Navratil[46] have shown from their experience that results are best when the two methods are utilized in combination, and either or both can at times be negative in early cancer. Biopsy and fractional curettage correlate cytologic and colposcopic findings but the histologic interpretation still remains decisive with respect to therapy. Colposcopy may best indicate where to take the biopsy, however, and thus assure a higher yield of positive "spot" biopsies.[37] Nevertheless, the circular or cone biopsy remains ideal when no specific or outstanding lesion is apparent, for adequate tissue is thus obtained for serial section and histologic study.[41] Furthermore, this type of biopsy, followed by endothermic desiccation, restores the diseased but benign cervix to normal status, as well as having eliminated cancer as a possibility in nearly every instance.

If abnormal epithelium is noted by colposcopy that has not been recognized by gross examination, then there is definite reason to carry out biopsy by either of the methods just mentioned. Whether it should be excisional as proposed by Hinselmann or just a sampling as advocated by Limburg is problematic.

Our impression is that colposcopy has too often been considered merely as a method of cancer detection and its potentialities disparaged by those with no experience, interest, or training in its use. The method has surely stimulated study of the normal cervix and its abnormal variations. It has stressed the concept of the transformation zone where the interplay of squamous and columnar epithelium takes place and in which location cancer may begin. This led Wespi to say that we should speak of squamocolumnar *junctions* rather than in the singular.[47] Since the transformation zone may occur in the endocervix, this might explain why early squamous lesions can occur there, as has been described by Gusberg[48] and others. It has also furnished evidence that carcinoma of the cervix may begin in multicentric areas, a factor recently reaffirmed by histologic studies.[49, 50] There is no definitive finding that distinguishes an intraepithelial from an early invasive lesion as far as colposcopy is concerned.

It is difficult to present a summary of this presentation without undue repetition. We have told the factual story of an experimental program in

colposcopy by a group of beginners, quoting freely from the experience and wisdom of others. From all this we offer the following conclusions:

1. Colposcopy is of value as an accessory method in the early diagnosis of cervical cancer, necessarily preceded by an astute history and meticulous pelvic examination. The Papanicolaou smear technique should be used in conjunction with the procedure for in this regard colposcopy may point to specific areas for solitary biopsies but it will never replace the latter for the definitive diagnosis upon which therapy depends. Neither can colposcopy eliminate the desirability of circular or cone biopsies to ensure microscopic study of all areas when indicated clinically. We have not diagnosed a single malignancy with the colposcope alone.

2. Colposcopy does give us a valuable method of visual education by virtue of the excellent magnification offered. This provides a much better concept of cervical abnormalities which in turn increases appreciation of the gross examination and its significance. Of additional value as a visual aid is the associated color photography made possible by the built-in Leica attachment. A wider acceptance of colposcopy seems desirable in view of the conclusions stated.

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Discussion

DR. KARL H. MARTZLOFF, Portland, Ore.—This discussion will be limited to a consideration of the colposcope. The examination of the cervix under low-power magnification with a conveniently mounted binocular dissecting prism permits many interesting observations otherwise not attainable. Particularly striking is the pulsation of the cervix in synchronization with the arterial pulse and the intermittent discharge of colorless secretion from cervical glands that open onto the portio through stratified epithelium. Also revealing is the varied appearance of the circumostial vermilion zone (so-called psuedo-erosion), particularly those areas that show a low polypoid structure, which to the unaided eye appear "granular" and are commonly misnamed granular, glandular, or papillary erosions.

The foregoing, when combined with carefully removed tissue for biopsy, are highly instructive and dispel much of the misconception conveyed by such long-utilized terms as "erosion," "psuedo-erosion," etc. These considerations alone make the colposcope a worthwhile instrument for teaching purposes, although for our discussion this is beside the point.

The real kernel, however, in this whole matter is what Hinselmann and his supporters have striven to accomplish and which Dr. Scheffey is also essaying, namely, the recognition of cancer on the portio of the cervix in its preulcerative stage.

The restrictive term preulcerative is used purposely, because it is well recognized by Hinselmann (1933) and his supporters that a bona fide benign erosion cannot be differentiated colposcopically from a small ulcerating cancer. Therefore, no matter how such a lesion is studied macroscopically, this becomes a dangerous academic sport unless it is combined with an adequate histologic investigation.

Now, in trying to recognize a benign leukoplakia, colposcopically, from one which possesses an intraepithelial carcinoid alteration, we find ourselves immediately involved in the problem of so-called cancer in situ and its macroscopic recognition. Also, we now are right back to the year 1907 with von Franqué who believed that cancer of the portio began as a leukoplakia and that an intraepithelial carcinoid alteration is merely a preinvasive stage of cervical cancer. These hypotheses were the stimuli for Hinselmann's study of the cervix under magnification in order to recognize cancer in a stage prior to ulceration or gross tumor formation, on the assumption that all cervical cancers at some stage appear as leukoplakia.

How successful these attempts have been has never been clear to me. I confess my continued reserve toward the claims that have been made by Hinselmann for the high incidence (20 per cent) of carcinomatous leukoplakias and for his blanket assumption (1930), never proved, that cervical cancer has an early stage when it appears as a leuko-

plakia. Also, the numerous published reports designed to implicate leukoplakias as commonly representing preinvasive stages of cervical cancer do not withstand critical analysis (Borst, Winter).

Further, in attempting to assess the earlier literature, mostly German, on this subject, it is often difficult to know what histologic criteria are utilized by some authors to define cancer. As a consequence the diagnosis of cancer made by one author has been seriously questioned or completely denied by other qualified workers (Winter, 1937). One, therefore unfortunately gains the impression of lack of objectivity, lack of critique, and a highly promotional effort on the part of proponents of the colposcope. In fact, it has been seriously proposed in the German literature that legislation be enacted compelling physicians who examine women under the German insurance plan to use the colposcope in all vaginal examinations.

We still do not know how to assess the more recent literature, because of the many personal and subjective factors that enter into macroscopic interpretations. Certainly, they lack the control and availability for review which histologic preparations and study permit. It still is difficult for me to be convinced from the literature that the colposcopically studied and reported cases of early cancer could not have been recognized by careful naked-eye observation.

We confess our strong attraction, initially, to Hinselmann's proposed use of the colposcope. However, we became less and less impressed by its value as our experience became more and more extensive. Our efforts to recognize cancer in a stage prior to tumefaction and ulceration extended over a period of ten years of regular critical use on approximately a thousand private patients selected for cervical abnormalities who could be followed and re-examined. During this interval we did not recognize with the colposcope a lesion that we did not initially notice and suspect of requiring biopsy on careful naked-eye examination under good illumination. Further, we have never observed a cancerous cervical leukoplakia. Since then (1940) our use of the instrument has been desultory.

More recently the emphasis on cervical leukoplakia has lessened, but the indispensability of the colposcope for recognizing early malignant change is still maintained by its promoters. The opinion has been expressed recently (Wespi, 1952) that colposcopy has been largely avoided in "Anglo-Saxon" countries because "histologists" either did not recognize or refused to recognize "preinvasive cancer," thereby leaving the clinical colposcopist in the dilemma of having his clinical impression of early cancer refuted by the laboratory. Certainly, this has not been my problem, nor has it been the problem of most of us. There is a more logical explanation for failure of the colposcope to achieve popularity, namely, that those who have used it have been unable to confirm the claims made for it. Our own experience is well reflected in a different way by the study of Limburg (1954) on 1,231 colposcopic examinations with biopsy. The colposcopic appraisal of benignity was incorrect in 192. Biopsy revealed "superficial cancer" in 61 and established cancer in 81. It is my impression that these areas would have aroused sufficient awareness merely on careful naked-eye appraisal to have prompted utilization of biopsy.

The cases of colposcopically studied carcinoma which Dr. Scheffey reports today do not impress me as affording any new evidence of the colposcope's indispensability for the recognition of early cancer. Unless his experience with the instrument is materially more favorable than ours, we do not contemplate its regular use again.

DR. EMIL NOVAK, Baltimore, Md.—It is really a rather curious phenomenon to note the sharp difference of opinion and practice as regards colposcopy which exists between the clinics of our Anglo-Saxon countries and those of continental Europe and, in recent years, those of South America. The method is used in almost all the larger clinics of Germany, Austria, and Switzerland. Its growing popularity in South American may be in part explained by the German training of a good many of the leading South American gynecologists. Shortly after Hinselmann's introduction of the method, Martzloff and, to a much lesser extent, a few others of us tried out the method, but the American literature on

colposcopy has been almost a complete blank until this paper which Dr. Scheffey has presented today. As he is good-natured and understanding, I do not think he will mind if I say that I do not think he made many converts today.

Although I do not personally know Hinselmann, I have been told by a colleague in Brazil, which he recently visited, that he appears quite resentful of the almost complete disregard of his technique in the English-speaking countries. This is what I meant by emphasizing the strangeness of the contrasting viewpoints. Many of us know such outstanding German and Austrian gynecologists as Antoine, Navratil, Limburg, and Wespi, all of them enthusiastic colposcopists, but also fine clinicians and pathologists. And yet Americans just take no stock in the method, though we believe that among them are also included some highly trained men. Some of us met and heard Limburg, of Hamburg, on his recent visit. Those with whom I've talked were impressed with his sincerity and his enthusiasm about colposcopy, but as yet I have not heard many express their intention to join the ranks of colposcopists. Perhaps the chief value of today's paper by Scheffey may be to impel us to ask ourselves whether we have too completely disregarded what may possibly be a worth-while part of the armamentarium in cancer detection. If any of us, after all these years, should take up colposcopy, a whole new and unfamiliar terminology will have to be learned, almost as tough a job as learning the jargon of psychiatrists.

Among other things, we would probably have to unlearn many of Hinselmann's concepts as to the precancerous significance of leukoplakia. In our own literature, this term, with its subdivision into Hinselmann's various groups and rubrics, has been almost completely supplanted by such terms as basal-cell hyperactivity of various grades, carcinoma in situ, and intraepithelial carcinoma. Incidentally, it is of interest that none of the innumerable authors who have written on these precursory or very early cancer lesions have stressed the frequency or importance of the keratinization which played such an important part in Hinselmann's description of leukoplakia.

DR. SCHEFFEY (Closing).—In the manuscript as published I think that you will be interested to see that we have *not* tried to make "converts" in any sense of the word. This has been an objective study without preconceived ideas because we had to learn personally about colposcopy from scratch after Lang and Tatarian visited Hinselmann's Clinic.

We give full credit to Dr. Martzloff for his straightforward position as he discussed it today, but I still stand by the conclusions arrived at from our experimental study, one of which is that the method per se will not primarily diagnose cancer of the cervix definitively. I stated this frankly.

I reaffirm the other conclusion also, that it has the advantage of teaching us to appreciate much more what we see with the naked eye, and for this reason I do not agree with Dr. Novak's criticisms. I also believe that the use of an instrument like this should achieve acceptance in educational institutions and hospital clinics especially. It has certainly stimulated the curiosity of interns, residents, staff members, and students in our institution, and anything that stimulates students to see and think for themselves, instead of just accepting what they are told, is, I think, a very good thing indeed.

THE EFFECT OF HYSTERECTOMY ON OVARIAN FUNCTION IN THE RABBIT*

B. TENNEY, M.D., F. PARKER, JR., M.D., AND S. L. ROBBINS, M.D.,
BOSTON, MASS.

IT IS generally recognized in the field of gynecology that there is a change in ovarian function in women following hysterectomy. While it may take years for the full effect, there is eventually a degeneration of ovarian follicles with possibly an increase in ovarian stroma. This concept is of importance, particularly in relation to indications for oophorectomy at the time of hysterectomy. No important study has been made of ovarian histology in the years following hysterectomy in the human. Such material is rarely seen, and then usually because of ovarian pathology. Certain hormonal studies have been made but they are none too conclusive.

In an attempt to throw some light on this subject, a study has been made on the effect of hysterectomy on the ovary and adrenal of the rabbit.

The normal rabbit ovary has a histological structure very similar to that of the human. Beneath the capsule there is an area of dense stroma filled with primordial and developing follicles. Beneath this layer is a less dense but typical ovarian stroma which contains no follicles but only blood vessels and fibrous tissue.

Following total hysterectomy in the rabbit, a definite and consistent change takes place in the histology of the ovary. For the first two weeks there is follicle stimulation and growth of the mature follicles. At the end of two weeks the follicles begin to degenerate and disappear. At this point, the fibroblasts throughout the ovary including all the stroma are replaced by large vacuolated cells which gradually take over the whole substance of the ovary. At eight to ten weeks, the follicles have largely disappeared, the ova are degenerating, and the whole ovary is composed of these large vacuolated interstitial cells, known as the interstitial body. If nothing further is done to the rabbit, this histological change becomes the permanent structure of the ovary. This interstitial change is similar to ovarian changes in the mated or pregnant rabbit or the female rabbit who has been even in the proximity of the male. However, in the mated rabbit there are also present many follicles which are active and normal. In addition, the change in the mated rabbit is temporary and the ovary returns toward normal histology. In the hysterectomized animal, the change is permanent. As the normal rabbit develops an interstitial body with advancing age, these changes probably indicate premature aging.

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When these ovarian changes were found to be a constant result of hysterectomy, the question immediately arose as to whether interference with the blood supply was the primary factor in the ovarian change or whether it was actually due to a change in the endocrine physiology or some other factor. In an attempt to solve this question, the blood supply to the uterus was tied off in several female rabbits. On sections of the ovaries at different intervals following this operation it was found that the interstitial changes in the ovaries did not take place. This seemed reasonable evidence that we were not dealing with the change due to interference with the blood supply.

Following this, a bilateral tubal ligation was done in a large number of rabbits. This was done by the Pomeroy procedure. Somewhat to our surprise, we found that the effects on the ovaries were identical with that of total hysterectomy. This again was as constant a finding as in hysterectomy. This change appears to be permanent also. Further support for the thesis that the ovarian changes were not due to interference with the blood supply were the results of ligating one tube only. Following such a procedure, the ovary on the side of the nonligated tube showed interstitial cell changes similar to those of the ovary with the ligated tube. This finding strongly supported the concept that the ovarian changes were due presumably to some fundamental endocrinological change and not due to interference with the vascular supply.

These findings suggest the possibility that the previous effect of hysterectomy on the ovary might not be due to the removal of the uterus per se but to the removal of the tubes which accompanies the operation.

After the development of the interstitial body in the ovary of the rabbit following hysterectomy and tubal ligation had been demonstrated, a study was made of the interstitial body itself. This was based on the reaction of the interstitial body to various hormones.

The first substance tried was Gonadophysin or pituitary extract. In the normal rabbit the ovary responds with a temporary development of hemorrhagic follicles, corpora lutea, and a marked growth of the interstitial body. In the hysterectomized animal the interstitial body is well developed. As long as active follicles are present they will respond to develop hemorrhagic follicles and corpora lutea. The injections may have stimulated the growth of the interstitial body.

The effects of chorionic gonadotrophin were similar to those of the pituitary.

Gonadogen or pregnant mares' serum was next injected in normal and hysterectomized animals. This hormone is assumed to be primarily a follicle-stimulating substance. In contrast to results with pituitary and chorionic hormone stimulation, there was a weak development of an interstitial body in the normal rabbit. The ovary did respond with the appearance of hemorrhagic follicles and corpora lutea. In the hysterectomized animal, Gonadogen appeared to have far less stimulating effect on the follicles than pituitary or chorionic hormones. No corpora lutea developed. In animals which had been given a course of follicle-stimulating hormone previous to hysterectomy and

then FSH after operation, there was a very slight development of the interstitial body. This certainly suggests that the absence of follicle-stimulating substance following hysterectomy or tubal ligation may well play a part in the development of the interstitial body and the degeneration of the follicle structure.

In addition to the histological study of the ovary following hysterectomy and tubal ligation, a study of adrenal histology has been made on the same animals.

Coincidentally with the previously described changes in the ovaries following total hysterectomy or tubal ligation, the adrenals show a marked increase in size due to thickening of the zona fasciculata. The degree of hypertrophy parallels the extent of the changes in the ovary. In addition, there appears another histological change. This occurs some four to five months following the operative procedures. The change consists in the appearance in the zona reticularis of large cells with a clear reticulated cystoplasm. As time progresses, a certain number of these cells are found also in the inner zone of the zona fasciculata.

In our opinion, there is a compensatory change in the adrenal gland for the changed physiology of the ovary. Hypertrophy of the suprarenal gland in rabbits following bilateral oophorectomy has been established.

In relation to this work, the growing interest of the gynecologist in the frequent appearance of functional bleeding in the human following ligation of the Fallopian tubes is of interest. This observation is consistent with the follicle change found in our study of the effects of tubal ligation on the rabbit ovary.

Summary

1. Total hysterectomy or tubal ligation causes marked changes in the ovary of the rabbit.

2. The changes are, first, follicle stimulation, followed in a few weeks by follicle degeneration and the development of the interstitial body.

3. The changes suggest a premature aging in the rabbit ovary.

4. A depression of follicle-stimulating hormone appears to occur.

5. Compensatory hypertrophy of the adrenal gland is a constant finding.

6. The appearance of a new and different cell in the zona reticularis of the adrenal is demonstrated.

Discussion

DR. JOHN ROCK, Brookline, Mass.—In 1949, S. R. M. Reynolds published the second edition of his thorough and scholarly consideration of the physiology of the uterus. In this splendid octavo volume he devotes eight pages to a chapter on the endocrinological effects of hysterectomy, and stiffens his statements with 83 references to worthy papers on the subject published between 1889 and 1947. In the introduction of this chapter, we read the following conclusion: "The effects of hysterectomy upon the ovary are today the subject of divided opinion, despite an abundance of clinical and experimental consideration by eminent clinicians and investigators for more than 60 years."

None will deny the clarification of human physiology by animal experimentation. However, it is also trite to say that results of this or that procedure in lower species are not

always indicative of similar, much less identical, results in Homo. After discussing the varied pertinent observations on the responsiveness of the ovary to the uterus, made by numerous biological and clinical investigators, Reynolds offers this added conclusion: "Because, moreover, ovarian activities are not abruptly terminated by removal of the uterine factor, it is clear that the uterus at the most exerts upon the fundamental hypophyseal-ovarian relationship a modifying effect which is blood-borne." In this statement, the "uterine factor" of which he speaks approvingly, is what he calls the "uterine hormone," but true to his enviable objectivity as a true scientist, he significantly shields the words within quotation marks.

Tenney and Parker maintain in this good report their reputation as accurate and unprejudiced observers whose appropriately open minds permit two quite nonspecific conclusions. One is that in the rabbit "the previous effect of hysterectomy on the ovary might not be due to the removal of the uterus per se but to the removal of the tubes which accompanies the operation"; the other, "that the absence of follicle-stimulating substance following hysterectomy or tubal ligation may well play a part in the development of the interstitial body and the degeneration of the follicle structure."

However abstruse may be the discoveries of what we call "pure science," we would all admit, I think, that the value of each of them ultimately resides in human welfare. As we extract from Tenney and Parker's observations of the role of the uterus and oviducts in the hypophyseal-ovarian axis in the rabbit we will keep in mind a possibly significant fact. In the rabbit but apparently not in man the gonadotropic activity of the anterior pituitary is markedly affected by afferent neurologic stimuli from the uterus. Perhaps these were involved in the techniques here so clearly reported? At first there was marked stimulation, then an absence of it. Dr. Tenney's extension of his own and of such studies as have been reported by Markee, Hollingshead, and Everett will be instructive.

I am indebted to Dr. Richard H. Grogan, Associate Surgeon on the staff of the Free Hospital for Women, for permission to give this prepublication statement of his findings in this analysis of 635 cases of women, under 40 years of age, who had had hysterectomies. In 390 of these cases one or both ovaries were conserved. Then, subsequently (for pain, dyspareunia, or a mass or cyst on the ovary) 20 of these 390 patients, all of whom had but one ovary, had the remaining gonad removed. He will report that 14, or 70 per cent, of these ovaries showed normal ovarian function as histologically demonstrated by presence of corpora lutea. In one patient the remaining ovary, eight years after hysterectomy, contained a normal fresh corpus luteum. In another instance the residual ovary was removed about fifteen years after hysterectomy and still showed normal function. I wish, in the name of our Society, I might thank Dr. Richard Grogan for his characteristic kindness in giving us this instructive information.

TABLE I. AGE GROUPS OF PATIENTS AT THE TIME OF HYSTERECTOMY

AGE	NUMBER OF PATIENTS	% OF GROUP
Under 25	2	10
25-30	7	35
30-35	7	35
35-39	4	20
Total	20	

TABLE II. INTERVAL BETWEEN HYSTERECTOMY AND OOPHORECTOMY

YEARS	NUMBER OF PATIENTS	% OF GROUP
0-1	3	15
1-2	5	25
2-5	4	20
5-10	7	35
Over 10	1	5
Total	20	

DR. WILLARD M. ALLEN, St. Louis, Mo.—The ovary of the rabbit is peculiar in that the stroma of the ovary is often literally replaced by cells which look in ordinary microscopic sections like slightly undersized lutein cells. The appearance of the cells, I suppose, made earlier observers suspect that they might be functional, hence the term interstitial gland. Some years ago when Dr. Corner and I were working on the isolation of progesterone we had the opportunity of seeing hundreds of ovaries from rabbits of virtually all ages. We had the impression that the older rabbits, presumably those that may have had several litters of young, were the ones which had the large gray, fragile ovaries such as Dr. Tenney has shown in his slides. This impression prompts me to ask a few questions: How long does it take after hysterectomy for the interstitial gland to develop? Also, the change in the adrenal glands is fully as striking as the change in the ovary. Rabbits, like other rodents, continue to grow in size for a long time after they reach sexual maturity. Was there any unusual increase in body size associated with the changes in the ovary and adrenal following hysterectomy?

Dr. Rock, quoting Reynolds, mentioned that there was much uncertainty regarding the effects of hysterectomy on ovarian function. With this I am sure we all agree. There is one aspect of the effects of hysterectomy in the rabbit about which there is little disagreement and that is this: When the uterus is removed in the pseudopregnant rabbit with functioning corpora lutea in the ovaries the corpora do not regress after two weeks of functional activity as they normally do, but on the contrary they persist for many weeks. It seems probable too that they are functional. Whether or not removal of the human uterus during the corpus luteum phase of the cycle would affect the regression of the corpus is a problem that has not been tackled as yet.

The stimulating effect of hysterectomy on the interstitial gland as shown by Dr. Tenney, and the early observation that hysterectomy prolongs the life of the corpora lutea in the rabbit again raise two fundamental questions. Why does the corpus involute in the nonpregnant animal when two hormonally paradoxical conditions cause the corpora to persist in the rabbit, namely, pregnancy and hysterectomy? Why does hysterectomy, and perhaps even tubal ligation, cause the appearance of the interstitial gland and hypertrophy of the adrenals? These questions are still largely unanswered.

DR. TENNEY (by invitation) (Closing).—Dr. Allen asked about the effects of hysterectomy in the human. This is a rabbit experiment and we take no stand about the effects in the human. We hope that the work will lead to an interest in the situation so that we may find out more about the human ovary. In some of the work of Dr. Olive Smith it has been suggested that there is some change in human endocrine physiology following removal of the uterus.

Dr. Allen also asked about the speed of formation of the interstitial body which is markedly increased over the normal progress of the ovary in the average rabbit. In our experience the average rabbit used as control does not show a well-developed interstitial body under a year and usually not for a year and a half. These changes appear very quickly in the animals operated upon; in six to eight weeks there is a well-developed interstitial body.

I cannot say anything specific about the effect of this procedure on the growth or size of the rabbit. We carried none of these rabbits for more than 18 months. They had been autopsied by that time and actually I cannot say that we noticed any difference in size or weight of these animals as compared to others.

In regard to the persistence of corpus luteum that Dr. Allen mentioned, we have seen that occur up to a year. I think this is another indication that in the rabbit something in his procedure affects the follicle-stimulating substance of the pituitary gland.

CORRELATION OF URINARY ESTROGEN-PREGNANEDIOL EXCRETION WITH UTERINE MOTILITY DURING PREGNANCY

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THIS study to determine the relationship of estrogen and pregnanediol excretion to uterine motility during pregnancy was initiated in 1951. There has been considerable work done by others on hormone excretion in normal and abnormal pregnancy[1-5] likewise, there has been extensive work done on uterine contractility during pregnancy.[6-8] There have been no studies designed to analyze the hormone excretion and uterine motility in the same patients from early pregnancy to delivery. We are reporting our findings concerning estrogen and pregnanediol excretion in normal pregnancy and its relationship to spontaneous uterine motility. In the course of this work we were fortunate in having obtained hormone and uterine motility studies from four patients who fell into spontaneous premature labor, and from three additional patients who developed pre-eclampsia. The uterine motility and the hormone excretion of the abnormal pregnancies present interesting departures from uterine motility and hormone excretion of normal pregnancy.

Method of Study

Patients were chosen from the prenatal clinic of the Colorado General Hospital for participation in this study. The only criteria for choice were: (1) pregnancy before the twentieth week and (2) a willingness on the part of the patient to cooperate in the collection of urine specimens and to report for the regular uterine motility recordings. Ninety patients volunteered for this project. Thirty-five of these failed to keep their appointments or moved from the community. Eight records are not sufficiently complete to report at this time. The motility studies were performed on 47 patients at two-week intervals from the twentieth week of pregnancy to delivery. Correlated hormone analyses were done on 17 of these 47 patients at the same two-week intervals. The types of patients studied appear in Table I.

Table I. Patients Studied

TYPES	MOTILITY STUDIES	CORRELATED HORMONE AND MOTILITY STUDIES
Normal full-term pregnancy	40	10
Spontaneous premature delivery	4	4
Pre-eclampsia	3	3
Total	47	17

*This study was supported by the Playtex Park Research Institute.

†Presented at the Seventy-eighth Annual Meeting of the American Gynecological Society, Quebec, Quebec, May 23, 24, and 25, 1955.

1. Collection and Assay of Urinary Estrogens and Pregnanediol.—

Patients were instructed to save all urine passed during the 24 hours immediately preceding the recording of uterine motility. The urine was voided into a bottle containing 200 ml. of n-butanol. The completeness of the 24 hour urine specimen was checked by means of creatinine determinations and all steroid hormone excretion values were corrected to correspond to the average 24 hour creatine output of the particular individual under investigation.

Assay of Urinary Pregnanediol.—The circumstances of this investigation were such that the urine specimens had to be stored for several months before they could be analyzed. It was found that, under these condition, determinations of sodium pregnanediol glucuronidate[9] were not valid. The determination of free pregnanediol by the Sommerville-Marrian[10] method also gave erroneous results with the urine of many individuals. Eventually a combination of the Sommerville-Marrian and Astwood-Talbot[11] methods was evolved which was supplemented by a digestion with petroleum ether. This method enabled quantitative recoveries of urinary pregnanediol to be obtained, and in almost all cases this pregnanediol was in a state of purity satisfactory for gravimetric estimation. Details of these methods are published elsewhere.[12]

Assay of Urinary Estrogens.—The urinary estrogenic steroids were liberated from their conjugates by acid hydrolysis and concentrated by a series of extractions with ether similar to those described by Engel and collaborators.[13] The estrogen concentrates were assayed colorimetrically by a modification of the Kober[14] assay suggested to us by W. M. Allen.[15] It was ascertained that no significant losses of estrogens occurred for at least sixteen months when urines were stored under butanol. Details of methods of estrogen analysis appear in another publication.[16]

2. Uterine Motility Recordings.—

Myometrial contractility was measured indirectly by an external tocodynamometer developed by Reynolds.[7] This device records from three strain gages, one placed near the fundus, a second over the mid-segment, and the third over the lower uterus. These abdominal wall gages are sensitive enough to register changes in the radius of curvature of the uterus beneath their circumference. They record both major and minor contractions without causing or recording extraneous motions such as maternal movements and fetal changes in position. The limitations of the tocodynamometer together with the advantages and disadvantages of any type of tocography are amply explained by Reynolds, Harris, and Kaiser.[8]

The week of pregnancy was determined from the last menstrual period and by physical examination. Each patient was placed in bed and the gages were taped to the anterior abdominal wall over the three segments of the uterus. Continuous recording was then done for approximately one hour. The first ten minutes of each record was excluded from the final tabulations because of the induced uterine motility coincident with maternal activity. Tracings were analyzed primarily for frequency of large contractions, their intensity, duration, time, and the work output in the upper, middle, and lower segments of the uterus. Correlative studies of total estrogens and pregnanediol in the urine and uterine contractility were then done after all data had been accumulated.

Results

Among the 47 patients studied, 40 patients delivered full-term infants. Ten patients with normal pregnancies had complete correlative hormone and motility measurements. From these 10 patients, 85 determinations each of pregnanediol and urinary total estrogens were done. The mean values for these urinary excretory products and their standard deviations were calculated. Toco-

dynagraphs from an additional 30 patients were included in the control group of uterine motility studies to give a total of 40 normal patients with 328 motility records.

1. Urinary Estrogen-Pregnanediol Determinations and Uterine Motility Associated With Full-Term Pregnancy.—

a. Estrogen-Pregnanediol Excretion in Full-Term Normal Pregnancy.— Ten normal pregnancies were studied from the twentieth to the fortieth week of pregnancy. Table II lists the mean values of urinary estrogens and pregnanediol in milligrams per day and the calculated standard deviation of the mean by weeks of pregnancy. Figs. 1 and 2 illustrate the gradual increase of estrogen and pregnanediol excreted in the urine from the twentieth to the thirty-eighth week. We were unable to demonstrate any fall in pregnanediol excretion during the last days or weeks of pregnancy. We did note a rapid rise in total urinary estrogens between the thirty-second and the thirty-eighth weeks of gestation.

TABLE II. SUMMARY OF URINARY ESTROGEN-PREGNANEDIOL EXCRETION* (10 FULL-TERM NORMAL PREGNANCIES, 85 DETERMINATIONS)

WEEKS OF PREGNANCY	NUMBER OF DETERMINATIONS	PREGNANEDIOL (MG./24 HR.)		ESTROGEN (MG./24 HR.)		P/E RATIO	
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
20	4	12.6	5.9	2.7	0.2	4.6	2.2
22	6	21.4	7.2	4.2	1.5	5.7	3.1
24	8	18.7	7.6	4.5	2.2	5.2	3.2
26	7	20.9	4.2	4.6	1.4	4.9	1.6
28	8	29.2	10.4	6.2	1.8	5.4	3.3
30	7	41.3	15.0	7.2	1.3	5.7	1.7
32	10	32.6	12.6	7.7	2.1	4.7	2.5
34	10	36.2	12.0	10.1	1.9	3.8	1.9
36	10	43.3	13.9	14.8	4.9	3.2	1.4
38	9	44.2	17.8	20.8	8.1	2.7	2.5
40	6	50.6	15.9	19.9	4.7	2.8	1.5

*Determined as free pregnanediol and total estrogen (Anker[12]).

TABLE III. SUMMARY OF UTERINE CONTRACTILITY (40 FULL-TERM PREGNANCIES, 328 RECORDS)

WEEKS OF PREGNANCY	NUMBER OF RECORDS	PER CENT OF PATIENTS WITH MAJOR CONT.	FREQUENCY PERCENTILES		INTENSITY PERCENTILES		WORK* PERCENTILES	
			50	75	50	75	50	75
20	21	24	0	0	0	0	0	0
22	24	25	0	0	0	0	0	0
24	32	38	0	1	0	34	0	0.7
26	32	25	0	0	0	0	0	0
28	35	29	0	1	0	13	0	0.3
30	33	42	0	1	0	38	0	1.3
32	36	44	0	2	0	31	0	1.0
34	37	59	1	2	27	44	0.6	2.0
36	35	63	2	4	34	49	1.0	3.4
38	30	60	1	3	30	66	0.8	4.0
40	13	54	1	2	20	41	0.2	2.1

*Work performed in the upper uterus in dynes per square centimeter calculated from formula: $W=(\frac{1}{3} I \cdot I + [D - T] \times F \cdot 1.073)$ (Reynolds[39]).

b. Uterine Contractility During Full-Term Pregnancy.—During normal pregnancy our recordings show that from the twentieth to the thirty-second week of pregnancy the uterus is relatively inactive. Fifty per cent of the toco-

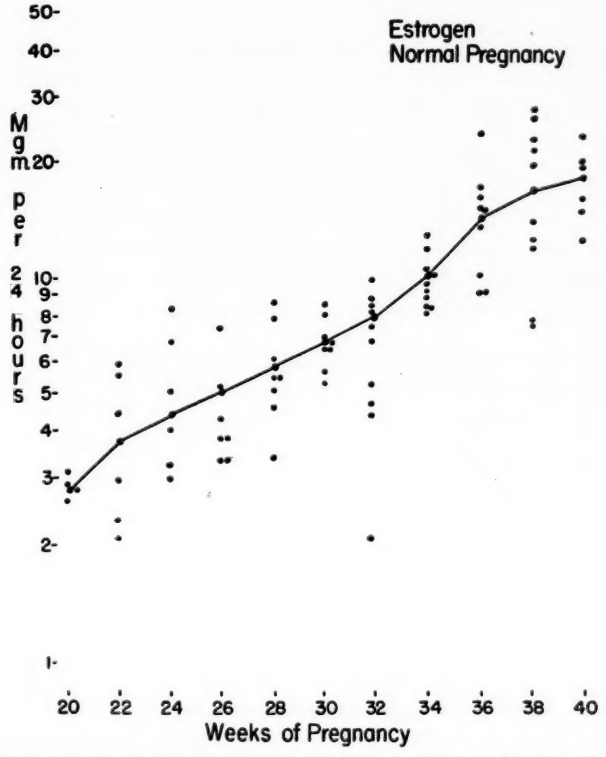

Fig. 1.—Total urinary estrogens obtained from 24 hour urine specimens, gathered at two-week intervals, from the twentieth to the fortieth week, in 10 normal pregnancies.

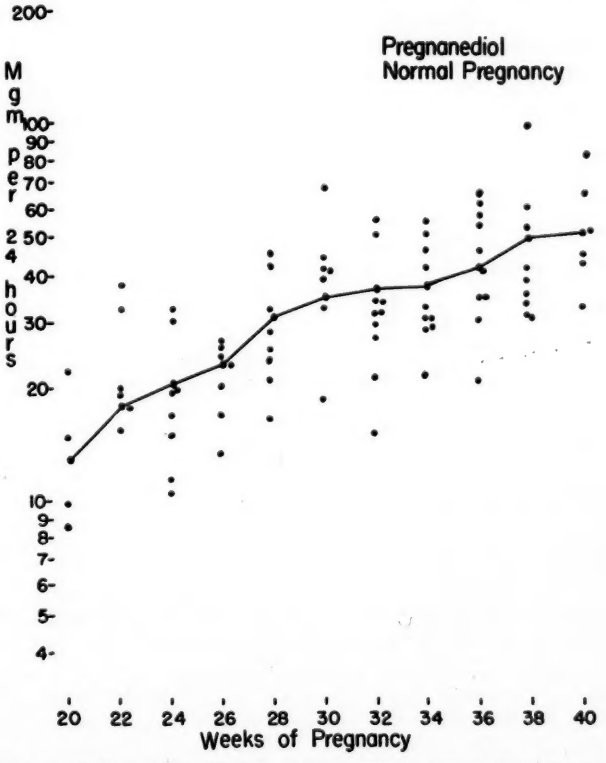

Fig. 2.—Pregnanediol excretion from 24 hour urine specimens gathered at two-week intervals, from the twentieth to the fortieth week, in 10 normal pregnancies.

dynagraphs showed no major or Braxton Hicks contractions up to the thirty-fourth gestational week. From the thirty-fourth to the thirty-eighth week the frequency, intensity, and work output gradually increased (Table III and Fig. 3).

c. Relationship of Urinary Estrogen and Pregnanediol to Uterine Motility in Full-Term Pregnancy.—An analysis of the uterine contractility patterns throughout full-term pregnancy appears to bear a relationship to urinary estrogen excretion. After the thirty-second week of pregnancy uterine motility increases. During this same period, urinary estrogens increase rapidly while the rise in pregnanediol is much less abrupt (Fig. 3).

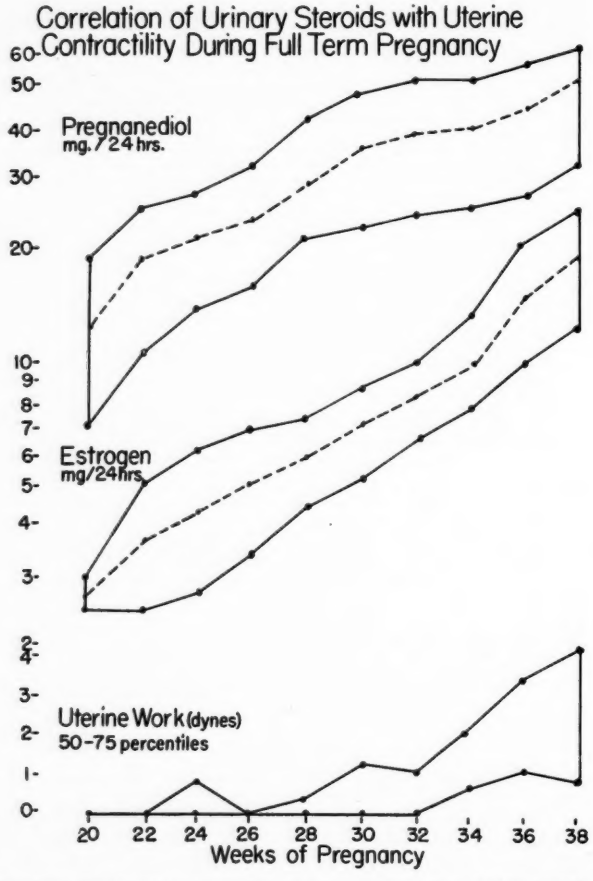

Fig. 3.—The broken lines represent the mean values for pregnanediol and urinary total estrogens from the twentieth to the thirty-eighth week for 10 normal pregnancies. The solid lines on the pregnanediol and estrogen portion of the graph represent the standard deviation for each gestational week. The uterine work graph represents the uterine motility results from 40 normal pregnancies. The upper line represents the seventy-fifth percentile while the lower line represents the fiftieth percentile.

2. Urinary Estrogen and Pregnanediol Determinations and Uterine Activity Associated With Prematurity—

a. Estrogen-Pregnanediol Excretion in Prematurity.—The total urinary estrogens in 4 patients followed from the twenty-fourth to the thirty-fourth week of gestation were analyzed. These patients had spontaneous premature delivery while in the study. Early in their pregnancy we had no method of predicting that these patients would deliver prematurely. Fig. 4 shows the general level of estrogen for the 4 patients who delivered prematurely to be less than our

mean values for those pregnancies that went to term. The general trend of low estrogen values associated with prematurity as illustrated in Fig. 4 and listed in Table IV is suggestive for all gestational weeks, but is statistically significant only at the thirty-fourth week of gestation. The mean level of total estrogens at the thirty-fourth week of pregnancies which went to term was 10.1 mg. per 24 hours with a standard deviation of 1.9, compared to 6.0 mg. with a standard deviation of 1.9 for the premature group at 34 weeks.

Pregnanediol excretion of patients who had spontaneous premature delivery shows no statistical or apparent difference in pregnanediol excretion when compared to that of patients who had term pregnancies (Table IV and Fig. 5).

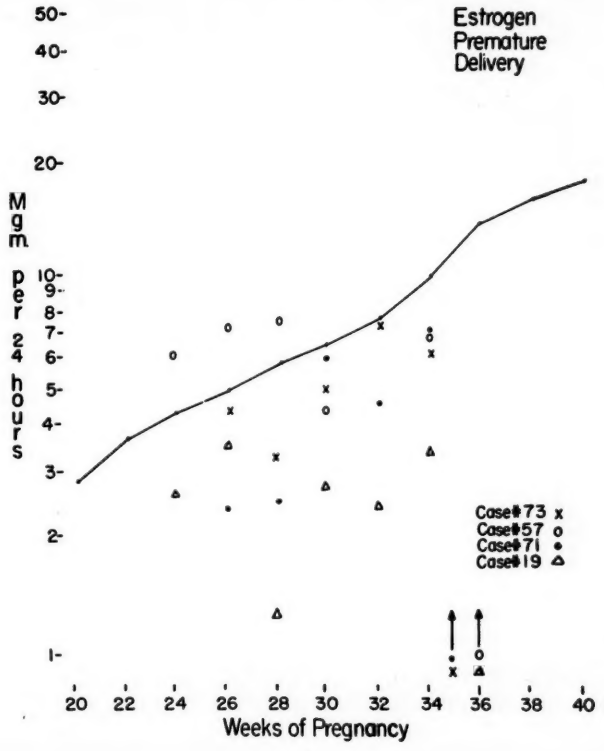

Fig. 4.—Urinary estrogens of 4 patients whose pregnancies ended in spontaneous premature delivery. The solid line represents the mean estrogen values found in our normal full-term pregnancy patients. The vertical arrows indicate date of delivery.

TABLE IV. SUMMARY OF URINARY ESTROGEN-PREGNANEDIOL EXCRETION IN 4 PATIENTS WHO DELIVERED PREMATURELY

WEEKS OF PREGNANCY	NUMBER OF DETERMINATIONS	PREGNANEDIOL (MG./24 HR.) CASE NUMBER				ESTROGEN (MG./24 HR.) CASE NUMBER			
		19	57	71	73	19	57	71	73
22	0								
24	2	16.4	34.2			2.7	6.3		
26	4	36.2	29.6	11.7	60.1	3.5	7.3	2.5	4.5
28	4	21.2	41.5	24.5	33.5	1.3	7.8	2.7	3.4
30	3	41.4		34.2	61.4	2.9		6.1	5.1
32	3	34.8		27.8	99.6	2.5		4.7	8.0
34	4	32.0	65.1	21.6	63.7	3.5	7.3	7.2	6.1

b. Uterine Contractility and Prematurity.—Reviewing the records of the patients who delivered prematurely and comparing these to the records of the full-term pregnancies, the following results were noted: uterine motility was hyperactive in each of the 4 patients (Table V); uterine activity was present in abnormal amounts as early as the twenty-sixth gestational week, eight weeks earlier than noted in the patients who went to term. These observations, while consistent for 4 patients who later delivered prematurely from no known cause, are not statistically significant because of the small number of patients with premature deliveries studied.

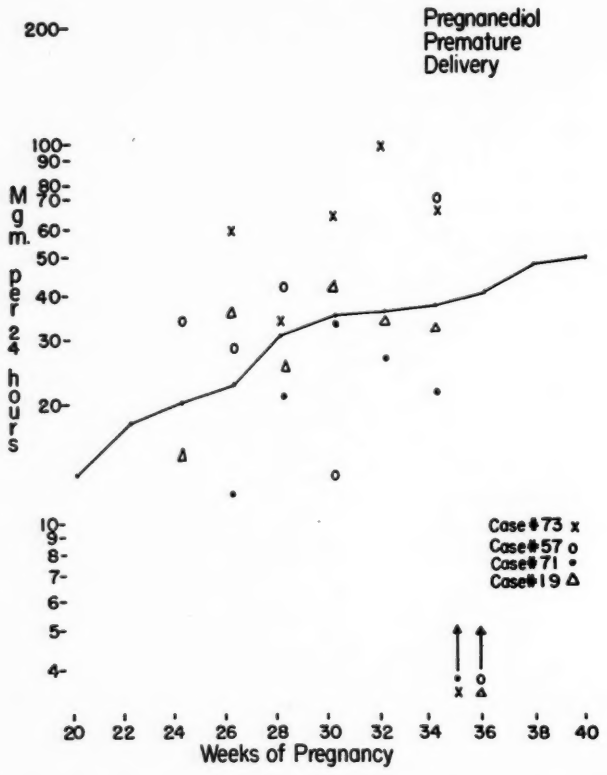

Fig. 5.—Pregnanediol values of 4 patients whose pregnancies ended in spontaneous premature delivery. The solid line represents the mean pregnanediol values found in our patients with normal full-term pregnancies. The vertical arrows indicate date of delivery.

TABLE V. SUMMARY OF UTERINE MOTILITY IN 4 PATIENTS WHO DELIVERED PREMATURELY

WEEKS OF PREGNANCY	TOTAL NUMBER OF RECORDS	WORK (DYNES/SQ. CM.) CASE NUMBERS			
		19	57	71	73
22	1	0.4			
24	2	0.9	1.1		
26	4	3.8	0.1	0	1.8
28	4	0	0.6	0.5	3.5
30	4	3.6	3.6	0.3	3.1
32	3	9.2		1.5	3.3
34	4	1.3	4.6	2.2	3.7

c. Relationship of Urinary Estrogen-Pregnanediol to Uterine Motility in Prematurity.—From this limited number of observations there is suggestive

evidence that low estrogen values may be associated with premature delivery. The total urinary estrogens, however, were relatively normal in one of 4 cases of spontaneous premature delivery. Pregnanediol values do not vary with uterine motility in the individual patient, and have no relationship to the premature onset of labor that we can measure or observe.

3. Urinary Estrogen and Pregnanediol Excretions and Uterine Activity Associated With Pre-eclampsia.—

a. Estrogen-Pregnanediol Excretion in Pre-eclampsia.—Three of our patients studied from the twentieth week of pregnancy to parturition developed pre-eclampsia. All 3 patients were normal pregnant women when initially enrolled in the study. Each of these patients demonstrated a low urinary excretion of estrogen and pregnanediol and later exhibited the classical signs of pre-eclampsia (Table VI, Figs. 6 and 7).

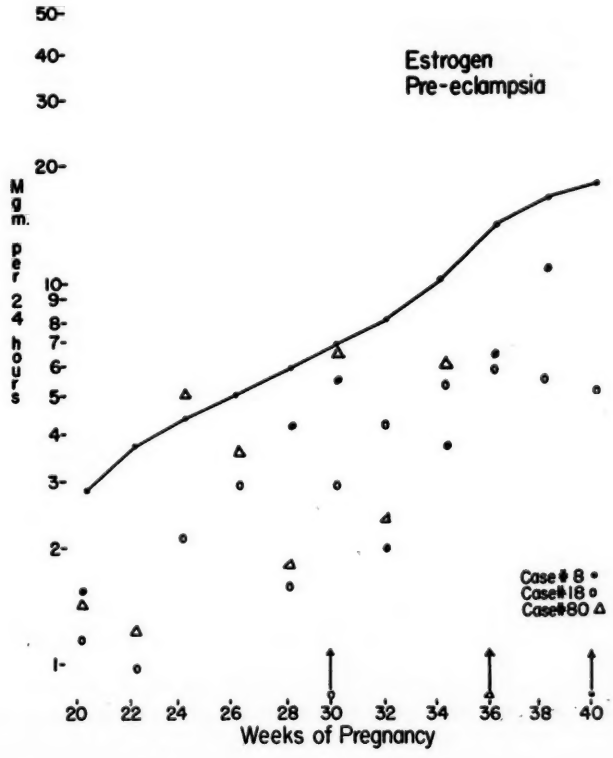

Fig. 6.—Urinary total estrogens associated with pre-eclampsia (3 patients). The solid line represents the mean estrogen values found in our patients who had normal full-term pregnancies. The vertical arrows indicate the point at which the first clinical signs of pre-eclampsia appeared.

Patient 18 was a 21-year-old multigravida. During the pregnancy under study, the patient first exhibited excessive weight gain at the twenty-second week, edema at the twenty-eighth week, albuminuria at the thirtieth gestational week, and hypertension at the thirty-second week. She was hospitalized on two occasions with suspected rupture of the membranes and premature labor. Her total weight gain during pregnancy was 38 pounds. At the forty-first week, after a six-hour labor, the patient was delivered of a 2,520 gram infant. Her blood pressure during labor and in the immediate postpartum period varied from 135/85 to 160/110. She has subsequently had a full-term normal pregnancy without signs of toxemia of pregnancy.

Patient 80 was a 22-year-old multigravida with a previous history of premature labor and a previous history of eclampsia. Near the thirty-second week of pregnancy the patient developed headaches and epigastric distress and at the thirty-sixth week was admitted because of edema, albuminuria, and hypertension. A diagnosis of pre-eclampsia was made. Labor was induced by artificial rupture of the membranes and the patient delivered a 2,230 gram infant spontaneously after a five-hour labor. Her blood pressure during labor remained near 190/120 and at discharge from the hospital was 140/108. She has not been seen since her hospital discharge.

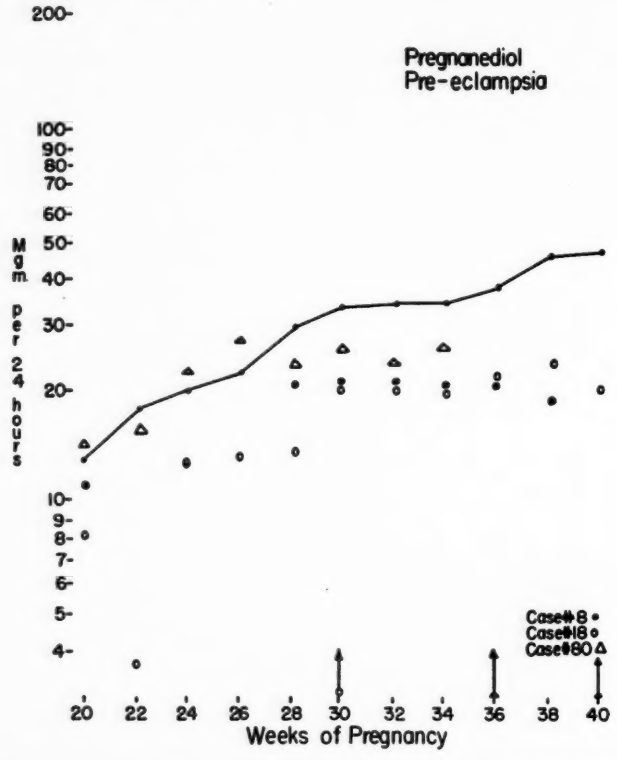

Fig. 7.—Pregnanediol values associated with pre-eclampsia (3 patients). The solid line represents the mean pregnanediol values found in our patients with normal full-term pregnancies. The vertical arrows indicate the point at which the first clinical signs of pre-eclampsia appeared.

TABLE VI. SUMMARY OF URINARY ESTROGEN-PREGNANEDIOL EXCRETION IN 3 PATIENTS WHO DEVELOPED PRE-ECLAMPSIA

WEEKS OF PREGNANCY	NUMBER OF DETERMINATIONS	PREGNANEDIOL (MG./24 HR.) CASE NUMBER			ESTROGEN (MG./24 HR.) CASE NUMBER		
		8	18	80	8	18	80
20	3	10.6	8.1	14.9	1.7	1.1	1.5
22	2		3.8	16.1		0.9	1.2
24	2		12.7	23.0		2.1	5.4
26	2		13.2	28.3		2.9	3.7
28	3	22.5	14.5	23.5	4.2	1.6	1.9
30	3	22.8	22.2	26.5	5.6	3.0	7.0
32	3	23.2	22.0	23.1	2.0	4.4	2.6
34	3	20.8	21.9	27.6	3.8	5.7	6.2
36	2	22.6	23.8		6.5	6.6	
38	2	19.4	25.7		11.2	6.3	
40	1		21.3			5.8	

Patient 8 was a 17-year-old primigravida. Her prenatal course was complicated by hypochromic microcytic anemia. She gained in weight from 97 to 123 pounds. There were no manifestations of pre-eclampsia before labor. During parturition her blood pressure increased from 132/90 to 150/110 and she developed albuminuria. She delivered a 3,050 gram infant without difficulty. The hypertension persisted until the fifth postpartum day; the albumin disappeared from the urine on the second postpartum day. Two years later this patient delivered a premature infant. The later pregnancy was uncomplicated by toxemia.

b. Uterine Motility Associated With Pre-eclampsia.—Unusually frequent contractions started in the toxemia patients between the twenty-sixth and the twenty-eighth gestational weeks; while the patients with full-term pregnancies did not show this much uterine activity until after the thirty-second gestational week. The recordings show that uterine irritability increased in the patients with toxemia to the termination of pregnancy (Table VII).

TABLE VII. SUMMARY OF UTERINE MOTILITY IN 3 PATIENTS WHO DEVELOPED PRE-ECLAMPSIA

WEEKS OF PREGNANCY	TOTAL NUMBER OF RECORDS	WORK (DYNES/SQ. CM.) CASE NUMBERS		
		8	18	80
20	3	0	0	0
22	2	0		0.3
24	3	0	0	0
26	2		0	1.7
28	3	0	2.7	1.4
30	3	4.3	0	4.2
32	2	0	3.7	
34	3	0	2.4	4.8
36	3	9.3	6.4	3.3
38	2		0	0
40	1		8.7	

c. Relationship of Urinary Estrogen-Pregnanediol Excretion to Uterine Motility in Pre-eclampsia.—In these 3 patients the low estrogen and pregnanediol values were associated with early and excessive uterine contractility (Tables VI and VII, Figs. 6 and 7).

Comment

1. Relationship of Uterine Motility and Hormone Excretion in Full-Term Pregnancy.—

Uterine activity occurring during pregnancy has been recognized both clinically and experimentally for many centuries. Mauriceau in 1660 described uterine contractions which preceded the onset of labor.[17] Oldham, Smith, Montgomery, and Priestly[18] gave an account of manually induced contractions in the human pregnant uterus ten years before J. Braxton Hicks'[19] classical description of spontaneous uterine contractions in 1872. A large number of investigators have studied the nature of spontaneous uterine motility during pregnancy and its relationship to the onset of labor. The more important contributions in recent years have been made by Murphy,[20] Alvarez and Caldeyro-Barcia,[21, 22] and Reynolds, Harris, and Kaiser.[8, 23] Uterine contractility was not associated with ovarian function until 1913.[24] Since that time many investigators in this country and abroad have shown the intimate relationship of the ovarian steroid hormones to myometrial contractility. A summary of this important work is given by Corner and Csapo.[25]

It appears from our study that when placental hormones (estrogen-pregnanediol) are being excreted in increasing amounts, the uterus is relatively free

of major uterine activity. After the thirty-second week, when estrogen excretion rises more rapidly than pregnanediol excretion, spontaneous uterine contractility increases markedly (Fig. 8).

The mechanism of the relationship between contractions of the pregnant uterus and the placental hormones has not been clearly defined, but studies at the cellular and molecular levels in skeletal and cardiac muscle have opened new approaches to the study of myometrial contractility.[26] Corner and Csapo,[25] by experiments using smooth muscle model systems, isolated muscle strips, and myometrium in situ, have found that estrogen governs the concentration of actomyosin (AM) in the uterine muscle, and regulates the quantities of adenosin triphosphate (ATP) and creatine phosphate (CP). The latter two compounds,

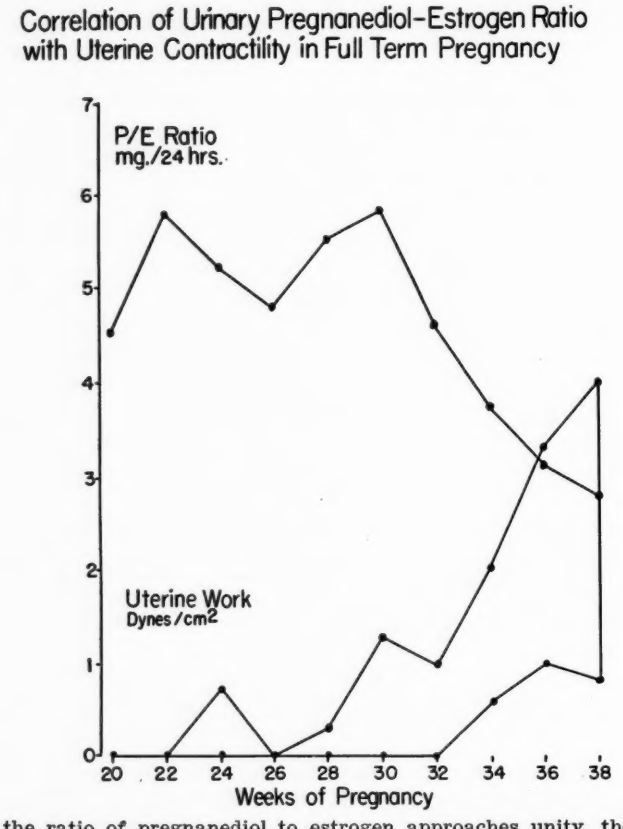

Fig. 8.—As the ratio of pregnanediol to estrogen approaches unity, the normal pregnant uterus undergoes a coincident increase in spontaneous physiological activity. The uterine work graph presents the fiftieth percentile on the lower line and the seventy-fifth percentile in the second line.

ATP and CP, are the immediate sources of energy for the contraction and relaxation of myometrial tissue. Csapo[27] suggests that progesterone influences potassium and sodium gradients across the cellular membrane and concludes that progesterone decreases the efficiency of the stimulus by decreasing activation and conduction. It is their belief that estrogen is probably responsible for the synthesis of the myometrial contractile system while progesterone is primarily responsible for regulating its excitability or rhythmicity.

The increased activity of the pregnant uterus during the last month of pregnancy is generally recognized, as well as the relationship of this activity to the placental hormones. Frank, Bonham, and Gustavson[28] in 1925 demonstrated

that estrogen was a necessary ingredient to uterine motility. Robson[29] in 1933 and Reynolds[30] in 1935 postulated that estrogen is the hormone responsible for the onset of labor. Reynolds[31] feels that the main objections to this theory are its simplicity and the fact that estrogen-induced motility in the nonpregnant uterus is a different pattern than that seen in the parturient uterus. He[32] further states, "It is not possible to activate the myometrium by estrogen when the uterus is under the influence of progesterone." Smith and Smith,[33] after studying estrogen and pregnanediol excretion during the last few weeks of pregnancy, state that there is estrogen and progesterone withdrawal from the uterus before labor. The placental steroids, according to these authors, are produced in smaller amounts and are subjected to increased destruction just before the onset of labor. Lyon[34] is of the opinion that a fall in pregnanediol excretion in the urine is an index to approaching labor. We are unable to shed any light on the hormonal relationships of the onset of labor but it does appear from our studies (Fig. 8) that at about the thirty-second to thirty-eighth gestational week there is a relative decrease in pregnanediol excretion which is accompanied by a measureable increase in uterine activity and an increased excretion of total urinary estrogens.

2. Relationship of Uterine Motility and Hormone Excretion to Spontaneous Prematurity.—

We have been interested in some of the more subtle causes of premature labor and delivery. Approximately two-thirds of premature infants are born from mothers who fall into spontaneous labor for no known reason. The question of hyperactivity of the uterus or insufficient placental hormones for continuation of the gestation has long been theorized. The present study of the relationship of hormone excretion to uterine motility in normal pregnancy provides us some insight into the physiology of premature labor from unexplained causes. Since all patients in this project were chosen for bimonthly hormone assay and motility studies early in pregnancy before prematurity could have been anticipated, the information gained is of particular value. Study of the uterine motility recordings of these patients discloses that as early as the twenty-sixth gestational week their uteri were excessively irritable (Table V). This observation was alluded to by Kaiser[23] in his uterine motility studies performed during pregnancy. Clinical observation corresponds to our recorded observations and Kaiser's reports; that is, patients who demonstrate or complain of unusual uterine activity from around the twenty-fourth to the thirty-second gestational week frequently do deliver prematurely.

It is of considerable interest that the premature group showed in the early weeks of pregnancy a relatively low excretion of total estrogens. When we encounter undue uterine irritability earlier than the thirty-second week of pregnancy accompanied by a persistently low excretion of urinary estrogens, we may be tempted to predict the premature onset of labor. Smith and Smith noted in 1941 that some patients had excessive uterine irritability with increased destruction of placental estrogens.[33]

3. Relationship of Uterine Motility and Hormone Excretion to Pre-Eclampsia.—

Low urinary estrogen and pregnanediol values in association with pre-eclampsia have been reported by Smith and Smith,[35, 36] and Taylor and Scadron,[37] Watts and Adair,[38] and others. Our findings of low estrogen and pregnanediol values in the urine of pregnant patients several weeks before the onset of the earliest clinical signs or symptoms of pre-eclampsia substantiates similar findings by Smith and Smith.[36] Our 3 patients who later developed pre-eclampsia were unselected pregnant women except for the fact that they were willing to cooperate for the study. Inspection of their records (Tables VI and VII and Figs. 7 and 8) will show that urinary excretion of both pregnanediol and estrogen

were distinctly reduced as compared to normal and that this constant low excretion of these two steroids was present long before the clinical signs of pre-eclampsia could be detected. Uterine irritability occurred unusually early in all 3 patients. Excessive uterine motility associated with pre-eclampsia is generally recognized. The ease with which labor may be induced in the pre-eclamptic patient as compared to the normal patient at the same gestational week is a common clinical observation.

Conclusions

1. Uterine motility as measured externally by the tocodynamometer increases rapidly after the thirty-second week in full-term pregnancy.
2. Total urinary estrogens increase markely after the thirty-second week of normal gestation.
3. Urinary pregnanediol shows only a gradual rise after the thirty-second week of term pregnancy.
4. When the ratio between pregnanediol and estrogen in full-term pregnancy approaches unity (between the thirty-second and thirty-fourth weeks) there is an accompanying increase in uterine contractility.
5. When pregnancy terminates in spontaneous premature delivery there appears to have been a reduced excretion of total estrogens in the urine from as early as the twenty-second gestational week. It is only at the thirty-fourth week that the reduced amount of estrogen is statistically significant when compared to the normal. More data will have to be accumulated for the other gestational weeks.
6. Pregnanediol excretion appears to follow the same pattern in term pregnancy as in spontaneous prematurity.
7. According to our limited experience, the uterus of the patient who delivers prematurely may demonstrate hyperactivity several weeks before premature delivery.
8. Urinary estrogens and pregnanediol were reduced throughout the last half of gestation in three patients who developed pre-eclampsia. The low levels of these steroid hormones were manifest several weeks before symptoms and signs of toxemia developed.
9. The uteri of the patients who later developed pre-eclampsia appeared to be more irritable than those of patients who had normal pregnancies.

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Discussion

DR. D. ANTHONY D'ESOPO, New York, N. Y. (by invitation).—Studies of the type presented here have interested the clinician because they seemed to offer the possibility of solving some of his most distressing problems. In them he hoped to find the key to the causes and prevention of abortion and of premature labor; to the means of dealing with toxemia, especially in relation to the time for optimal interference based on laboratory data that might reveal the status of placental function, and, finally, to a clearer understanding of the many disturbances of female genital physiology.

After considerable work that started about twenty years ago, however, there has been a loss of much of the original impetus; so it is refreshing to see the renewed interest evidenced by this contribution.

The waning of interest has been due to several factors. Of these, the most important has been the conflicting data that have been reported. A review of the literature leaves one with the impression that either a variety of dissimilar conditions that were erroneously thought to have a common basis were grouped and studied as entities, or the chemical methods variously used yielded different substances for assay. The impression of the steroid experts is that our present methods do not reflect a precise relationship to the nature and amounts of the mother substances secreted. This is not a criticism of the methods used by Dr. Taylor, but rather a plea for more basic work in this important field of biological chemistry. The spectrophotometer offers a new and perhaps rewarding approach.

Referring more specifically to the results of this prodigious amount of work, I want first to congratulate the authors on the conservatism they have shown in the interpretation of their results. Their findings have been factually stated without the fanciful speculations that often form the large part of endocrinological presentations.

The data obtained with the tocodynamometer confirm what has been known to be true from clinical experience and add little to the main body of the material presented.

The amounts of pregnanediol and estrogens found before the onset of normal labor showed no tendency to diminish from a previous peak level. This both agrees and disagrees with the work of other investigators. This conflicting evidence may be either an expression of the different methods used or may indicate that the steroid hormone levels at the onset of labor are variable. There is still the possibility that a hormone shift occurs rapidly and becomes elusive unless determinations are made daily. That there might be considerable variability of the hormone levels at the onset of labor is suggested by Dr. Taylor's material by the rather wide variations of hormone content in similar groups of patients. Even more suggestive is the finding of quite different hormone patterns at the onset of normal labor, of premature labor, and of labor in toxemia. Perhaps this all means that there is no specific balance of these hormones when labor starts or, to put it another way, the onset of labor is not hormonally controlled. Clinical experience is suggestive of this. We are all familiar with the initiating effect of hemorrhage, of overdistention, and, at times, of premature rupture of the membranes. In the latter group, I refer especially to those cases of premature labor in which the premature rupture of the membranes seems to force an apparently unwilling uterus into prolonged and dystocic activity.

While these differences in hormone balances preceding labor may seem confusing, they may point to the fact that there are different trigger mechanisms for initiating labor. It does not necessarily follow that similar chains of events are due to similar causes.

The reduced steroid values observed in toxemia conform to those reported in some of the other studies. What do these low values mean? Are they in some way related to the cause of toxemia, or do they more simply represent an effect of the disease? Attempts to relate them to the etiology of toxemia have thus far received no confirmation. It seems more likely that the diminished steroid output is another expression of this disease with so many facets. It may be simply the result of a decreased placental function or of alterations in the way the diseased body handles them. We have been impressed with the low (and in one case zero) values of pregnanediol when the pregnant woman with Addison's disease goes into a crisis. With recovery, the values return to normal. This suggests that profound metabolic disturbances, such as occur in toxemia, may interfere with the secretion, storage, conjugation, and clearance of these substances. The alterations of steroid metabolism in the complications of pregnancy require more basic study. Experiments designed to show the fate of tagged steroids administered to toxic and normal pregnant women might clarify the differences, if any, that exist in the metabolism and excretion of these substances in health and disease.

DR. EARL T. ENGLE, New York, N. Y. (by invitation).—Dr. D'Esopo has given the consensus the interest of our group in this matter. Perhaps I may again express our attitude by saying that at the present time we are doing no pregnanediol studies. Dr. Lieberman, who is a very good steroid chemist, says the methods are not adequate. We have a number of studies ready to run and he says the limits of the method are such that we shall have to wait until the chemist develops new ones for measuring these excretion values. The problem of estrogen I think is more complicated than of pregnanediol. For twenty years we have been trying to do estrogen excretion determinations and, as you know from the literature, the results are extremely variable. I personally see no future until we get new methods for the elucidation of these findings. I am interested in Dr. Taylor's study but I do not think that at the present time we have adequate methods for continuing along this line.

DR. GEORGE V. SMITH, Brookline, Mass.—The work Dr. Taylor reports confirms our findings in every respect. There is only one aspect in which our results seem to differ, and this is more apparent than real. I refer to the matter of urinary pregnanediol prior to premature labor. In this situation Dr. Taylor, using a colorimetric method that measures pregnanediol only, failed to find any evidence for progesterone deficiency. The gravimetric method of Venning, which measures a combination of progesterone metabolites, has consistently, in our hands, prognosticated premature labor as well as late pregnancy toxemia. In a number of pregnancies we have followed weekly urine specimens by both methods. In one case, values for pregnanediol alone, colorimetrically measured, failed to give any indication of impending trouble; whereas the curve for pregnanediol calculated from the glucuronide

complex, as measured by the Venning method, had been below normal for eight weeks prior to any clinical evidence of abnormality. It may be that if Dr. Taylor had used the Venning method, he would have confirmed our evidence for progesterone as well as estrogen deficiency prior to premature labor.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—At this moment it would seem worth while to emphasize a point which Dr. Taylor made in his paper and which was also remarked upon by Dr. D'Esopo, namely, that the findings of decreased estrogen in premature labor and pre-eclampsia are not necessarily the cause of these conditions but are reported simply as related findings. There is nothing in this presentation to support the thesis that there is a cause and effect relationship between the two.

Again, as was remarked by Dr. D'Esopo, the structural and biologic changes which take place in the placenta are very possibly the common denominator both of decreased estrogen production and of premature shortening of pregnancy.

We are not justified therefore in assuming that the treatment of premature labor and the treatment of pre-eclampsia lie in the supplementing of those hormones which are found deficient in this syndrome complex; at least there is nothing in this thesis to support that point of view.

A great deal more needs to be learned concerning the delicate structural and biologic relationship between the fetal portion of the placenta and the closely adjacent decidua and maternal myometrium before we can safely conjecture upon what factors give rise to either normal labor at term or premature interruption of pregnancy in toxemia.

DR. TAYLOR (Closing).—I wish that Dr. Engel had spent more time on the discussion of methods. What he has to say corresponds to my own experience in engaging men to do this analysis work. They often say that they want to spend all their time improving methods. Our laboratory is engaged in the study of improved methods of hormone analysis, but at the same time we feel that existing methods are sufficiently accurate to use in a study of this type. There may be estrogens that are not being separated by current methods, but if these estrogens are escaping, they are escaping in consistent amounts for each test. Our methods given consistent results in our laboratory. Control studies are always parallel.

We did not use the method Dr. Smith suggests for pregnanediol determinations because our specimens were stored under butanol for several weeks before analysis. Under these conditions, Dr. Smith's method is not suitable.

Dr. Montgomery spoke of the role of the placenta in our results. The patterns of hormone excretion in the patient with premature delivery or eclampsia are, I believe, a reflection of placental insufficiency from one cause or another.

SURGERY AND RADIOACTIVE GOLD TREATMENT FOR CARCINOMA OF THE OVARY*

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IN THE past few years, radioactive colloidal gold has come into use in the treatment of ascites resulting from metastatic neoplasm. This is a preliminary report and evaluation of the clinical results of the prophylactic and palliative use of radiogold in 28 cases of ovarian carcinoma treated from January, 1952, to March, 1955. Other purposes of this report are: (1) to clarify the indications and limitations of the uses of radiogold; (2) to describe our technique and experience; and (3) to compare the clinical results with those obtained in the "conventional" treatment of ovarian malignancy, that is, surgery followed by external irradiation.

The purpose of gold administration is to deliver ionizing radiation directly to the serous tissue implants with a minimum of radiation to normal tissue, or to the hemopoietic and gastrointestinal systems. Gold (Aurcoloid—198†) is suitable for this purpose because of its physical, chemical, and colloidal properties. The physical half life is 2.7 days. It has beta radiation with a maximum range in water of 3.8 mm.; and gamma radiation of 0.41 mev. The gold is chemically inert.

When the radioactive colloidal gold, distributed in a suitable amount of isotonic saline solution, is instilled into the peritoneal cavity, the gold "plates" out on the serous surfaces by a process of absorption and phagocytosis so that the radioactive material disappears from the free fluid in the cavity. Fifty per cent of the radioactivity is removed from the free fluid in from 24 to 48 hours. By these mechanisms the radioactive material is placed in intimate contact with the malignant cells and delivers radiation to them.

The basic problem of dosage is to administer sufficient radiation to produce the desired therapeutic effect without inducing serious damage to normal tissue or severe systemic reactions. Doses as high as 225 mc. in the peritoneal cavity have been tolerated without complication and doses as low as 100 mc. have produced palliation. The average dose used is about 160 mc. in a single intraperitoneal administration.

Indications

One of the complications of metastatic ovarian carcinoma is the recurrent accumulation of fluid in either the peritoneal or pleural spaces or in both. The

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†Radioactive colloidal gold, Au^{198}, was supplied by Abbott Laboratories, North Chicago, Ill.

repeated removal of the fluid is of short benefit to the patient and at the same time depletes the body of essential fluids and protein. Either or both serous cavities may respond to radiogold treatment. Although the transport of colloidal material from one serous cavity to the other has been demonstrated by us, the amount transferred is insufficient to produce a therapeutic effect in the untreated cavity.

The exact mechanism by which the fluid is produced in metastatic malignant disease of serous cavities has not been satisfactorily explained. Recently Straube and co-workers have shown experimentally that altered vascular permeability may be a factor contributing to the accumulation of peritoneal fluid. Andrews and associates have observed a disappearance of free tumor cells from fluids aspirated after the patients were treated with radiogold. This would indicate that a biologic change can be induced so that the formation of fluid in the serous cavity is decreased or completely inhibited after a single intracavitary injection of radiogold.

Cases considered suitable for this type of treatment may be classified into two groups: (1) palliative and (2) prophylactic. The primary purpose of the treatment in the palliative group is to inhibit the reaccumulation of fluid in the abdomen where the fluid is already present as a complication of the malignancy. In the prophylactic group, there was evidence at the time of operation of residual malignancy such as small peritoneal implants or the rupture of a malignant cyst during operation, introducing malignant cells into the peritoneal cavity. The purpose of the gold treatment in this latter group is to decrease the possibility of implantation of the malignant cells by the destruction of free-floating cells at a time when they are most vulnerable to the short-range beta radiation.

In considering a patient for gold treatment, a careful evaluation of the patient's general condition, blood count, the presence or absence of large intra-abdominal masses, and the rate of fluid accumulation is made. The over-all evaluation of the intracavitary radiogold is made difficult when it is given in terminal cases. The general condition of the patient should warrant the use of this method as a palliative or prophylactic rather than as a heroic measure.

Administration and Technique

Concentrated gold colloid in a sterile vial is brought to the point of delivery in a heavy lead shield. Approximately 200 c.c. of sterile isotonic saline solution is used to flush the colloidal gold material from the shielded vial into the peritoneal cavity. The gold may be administered following a paracentesis, or may enter the cavity by means of a small laparotomy and introduction of a polyethylene tube. Special equipment has been devised to ensure rapid administration of the gold thereby minimizing the radiation hazard to personnel.

Radiation Hazard to Personnel Administering Gold.—Radiation hazard to all personnel concerned with the administration of the radioactive gold must be carefully evaluated and protective measures taken to ensure that the dose received by occupational personnel remains within permissible limits (300 milliroentgens per week). The most effective means of protection are distance from the source, speed of operation, and shielding of the source. Personnel who

administer the radioactive gold wear pocket ionization chambers and film badges throughout all phases of the preparation and delivery of the gold to the patient.

Radiation Hazard to Nursing Personnel and Visitors.—Careful consideration must be given to the exposure of nursing personnel and visitors in the postoperative care of the patient. A survey of the radiation field in the vicinity of all patients with radioactive gold is routinely made. The following regulations will in general keep the exposure of personnel within permissible limits:

1. Rotation of nurses and nurses' aids so that one individual does not bathe the patient more than once during her stay.
2. With other patients in the room, the beds should be approximately nine feet apart.
3. Bedside visitors limited to two hours per day during the first three days.

Side Reactions and Precautions.—Basically, reactions to the gold therapy can be divided into two types: (1) clinical reactions and (2) laboratory reactions. The clinical reactions may appear in the form of nausea, vomiting, diarrhea, anorexia, presumably due to irradiation of the gastrointestinal tract. The laboratory reactions may be evidenced by lymphopenia followed by a mild depression of the granulocytes and thrombocytes. Rarely, a severe leukopenia or anemia may develop following therapy with radioactive gold.

Results of Therapy

In order to compare the results of gold therapy with those of the conventional treatment, a survey of ovarian malignancies encountered during a five-year period at the Milwaukee Hospital was undertaken. Special studies were made of the histopathologic types of ovarian carcinoma and the incidence of ascites as an associated complication.

During the five-year period ending Dec. 31, 1953, there were 5,616 gynecologic patients admitted to Milwaukee Hospital for diagnosis and treatment. Ovarian tumors, not including follicle and corpus luteum cysts, made up 512 of the diagnoses. Malignant ovarian neoplasms accounted for 57, or 11.1 per cent. There were 370 genital malignancies found in these 5,616 patients and since 57, or 15.4 per cent, were located in the ovaries, it appears that ovarian malignancy is second in frequency only to endometrial and cervical carcinoma.

TABLE I. INCIDENCE OF OVARIAN NEOPLASMS, 1949-1953

Gynecologic cases		5,616
Ovarian tumors	512	
Malignant	57	(11.1 per cent, or 1.2 per cent of all gyn. admissions)
Genital tumors		
Malignant	370	
Ovarian malignancy	57	(15.4 per cent)

The pathological diagnoses of these 57 ovarian malignancies are shown in Table II.

TABLE II. PATHOLOGIC DIAGNOSES OF OVARIAN MALIGNANCIES

Serous cystadenocarcinoma	30
Adenocarcinoma	11
Pseudomucinous cystadenocarcinoma	10
Carcinoma	2
Krukenberg tumor	2
Granulosa-cell carcinoma	1
Squamous-cell carcinoma arising in benign teratoma	1

A great majority of these patients were treated by surgery. Whenever possible, the conventional total hysterectomy and bilateral salpingo-oophorectomy were performed. Where the diagnosis of ovarian malignancy was made by the pathologist on an excised ovary, the remaining ovary was subsequently removed along with a total hysterectomy. Occasionally omentectomy was done in conjunction with these procedures. In addition, deep x-ray therapy to the pelvis, lower abdomen, and frequently the upper abdomen was utilized.

Only 14 of these 57 patients had ascites at the time of hospitalization or subsequently developed the condition. This is an incidence of 24.6 per cent. Pearse and Behrman found that 32 per cent of their group showed ascites. Eight of the 14 patients previously mentioned were treated with surgery and external irradiation while the remaining received radioactive gold in addition to surgery and irradiation. Approximately one-half of these patients are alive; 21 are dead and 6 have been lost to follow-up.

There were 28 cases of ovarian carcinoma treated by the administration of radioactive colloidal gold during the two-year period from Jan. 24, 1952, to Dec. 31, 1953, with follow-up to March 31, 1955. This period was selected to include the earliest cases treated and to permit a minimum of 12 months' follow-up on the most recent cases. The patients were referred to the Marquette University Isotope Department for treatment by their personal physician primarily because conventional treatment had failed to control the disease or its symptoms. In all cases the gold was administered by Isotope Department personnel in cooperation with the attending physician or surgeon at several hospitals in the Milwaukee area affiliated with the Isotope Department in this project. The tabulation of these cases according to histopathology of the primary tumor is presented in Table III.

TABLE III. CASES TREATED WITH RADIOACTIVE COLLOIDAL GOLD, 1952-1954

Serous cystadenocarcinoma	17
Adenocarcinoma	6
Granulosa-cell carcinoma	3
Carcinoma	2
Total	**28**

TABLE IV. COMPARISON OF TREATMENTS

	CONVENTIONAL TREATMENT—NO GOLD, 1949-1955			TREATMENT WITH AU^{198} IN ADDITION TO CONVENTIONAL TREATMENT, 1952-1955		
		ASCITES	AVERAGE TIME (MONTHS)		ASCITES	AVERAGE TIME (MONTHS)
Serous cystadenocarcinoma	10 living	0	44.8	4 living	1	19
	13 dead		11.6	13 dead		10.5
	With ascites	4	5.0	With ascites	11	8.3
	Without ascites	9	13.1	Without ascites	2	22
Adenocarcinoma	7 living	1	27	1 living	1	30
	1 dead	1	4	5 dead	3	5.6

It may be possible to compare the results obtained by the conventional treatment alone with that where radioactive gold has been added. Such comparison in Table IV shows that of 23 patients with serous cystadenocarcinoma treated by surgery and x-ray, 10 are living approximately 45 months; 13 are dead (4 died with associated ascites at an average of 5 months and 9 without

ascites in 13 months). When colloidal gold was added to the conventional treatment of 17 patients, 4 are living an average of 19 months and 13 are dead (11 with ascites living 8.3 months and 2 without ascites 22 months.) It must be realized that the patients with ascites generally were in an advanced stage of the disease; therefore, one may expect a considerable reduction in longevity. A similar comparison was made in the adenocarcinoma patients as shown in Table IV. Here we find, likewise, no increase in longevity because of the addition of radioactive gold.

It is impossible to compare the patients whose ovarian tumors were diagnosed as pseudomucinous cystadenocarcinoma because none were treated with radioactive gold during the interval studied. With conventional treatment, however, 7 of these patients are living and well on the average of 35 months following operation. Only 1 of these had ascites at the time of surgery.

TABLE V. CASE SUMMARIES OF PATIENTS TREATED WITH RADIOACTIVE COLLOIDAL GOLD

CASE NUMBER	AGE	DOSE Au^{198} MC.	NUMBER OF TAPS BEFORE GOLD	NUMBER OF TAPS AFTER GOLD	SURVIVAL
Papillary Serous Cystadenoma.—					
730	67	217	1 (2 gallons)	0	Living 42 months
1263	63	140	0	0	Living 14 months
1531	45	162	0	0	Living 6 months
1040	46	220	0	0	Living 24 months
546	63	130	0	0	Died 20 months
577	61	150	1	0	Died 1 month
657	45	190 192	125	75	Died 35 months
689	74	188	0	0	Died 24 months
693	52	194	1	0	Died 2 months
766	72	192	1	0	Died 5 months
770	78	183	1	0	Died 2 months
951	69	219	4	0	Died 8 months
981	54	200	3	0	Died 13 months
1059	54	224	1	0	Died 4 months
1187	65	110	1	0	Died 10 months
1434	47	159	3	5	Died 9 months
1500	60	160	1	1	Died 4 months
Adenocarcinoma.—					
771	38	180	0	0	Died 4 months
818	49	171	0	0	Died 14 months
1142	47	150	5	1	Died 1 month
1242	41	110	1	3	Died 8 months
1386	61	154	1	0	Died 1 month
789	50	175	0	0	Living 30 months

There is no question but that radioactive colloidal gold administered prophylactically and therapeutically for the prevention and relief of ascites in the 28 patients reduced and often eliminated the necessity of subsequent

paracenteses. This is well illustrated by Table V which lists the case studies of 23 of these patients. The table shows that 10 patients who had ascites and required taps before gold, did not require taps after a single administration.

Evaluation of the treatment on a statistical basis is difficult because of the small number of cases related to each classification of histopathology and the fact that in a large proportion of the cases in which gold is used, the patient has the ascites which is an indication of advanced disease. Since the patients' personal physicians are in the best position to give a clinical impression of the effect of the gold treatment on their patients, their statements as to the clinical effect of the treatment have been tabulated in Table VI.

TABLE VI. CLINICAL IMPRESSIONS OF PATIENTS' PERSONAL PHYSICIANS

FAVORABLE		UNFAVORABLE		NO COMMENT	TOTAL
No complications following gold therapy	19	Some complications following gold therapy	4	5	28
Benefit to patient from treatment	19	No benefit to patient from treatment	5	4	28

The preponderance of clinical impression is that the course of the patient was favorably influenced by the administration of gold in that it was felt that there was increased comfort, respite from repeated aspirations, and reduction in the rate of fluid formation. The table also shows that, clinically, the patients did not experience significant distress due to the treatment. On the basis of such subjective evaluation, the palliation achieved seems to outweigh the ill effects which might be induced by the treatment.

Summary

The incidence of ovarian neoplasms in a hospital caring for only private patients is 9.1 per cent. Only 11.1 per cent were malignant. This is a much lower incidence than is frequently reported. However, it represents a truer picture of the frequency of malignancy than do the reports that come from hospitals where the patients, for the most part, are indigent.

Ascites was present in 24.7 per cent of the patients with ovarian malignancies.

It is quite obvious that no great claim can be made for the therapeutic effect of radioactive gold following the usual conventional treatment for ovarian neoplasms. It should be realized, however, that the disease was frequently much farther advanced in the patients treated with radioactive gold than in those treated by the conventional methods alone. It is our opinion that the radioactive gold did have a very definite deterrent effect upon the production of ascites. That radioactive colloidal gold introduced peritoneally was not harmful to the vast majority of patients is attested to by the favorable comments from the many attending physicians.

The reason for supplementing the conventional method of therapy for ovarian carcinoma with gold is that the final results indicate such a therapeutic procedure to be warranted on the basis of palliation as measured by the clinical impression rather than by statistics.

It is not possible to compare results obtained by the conventional method of treatment of ovarian malignancy with that of the additional or augmented

therapeutic procedure of intraperitoneal gold because: (1) The patients selected for gold therapy were chiefly those who have developed ascites which is a clinical evidence of widespread malignant disease. (2) The presence of ascites is also an indication of a very highly malignant form of ovarian carcinoma, although this may not be indicated by its histopathology.

It is planned to continue this study to acquire a larger series of cases with a longer follow-up, which may possibly improve statistics, along with a refinement of technique and a more critical group of criteria for selection of cases to be submitted to the gold therapy.

Many investigators have reported the use of radioactive gold in the treatment of ascites associated with ovarian malignancy, failing to specify the histologic type of primary tumor. A better correlation between the effect of radioactive gold and specific types of malignant tumors of the ovary may lead to a better understanding of the disease and its therapeutic management.

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Discussion

DR. JEAN P. PRATT, Detroit, Mich.—In such a dark field as carcinoma of the ovary, anything that gives a ray of hope is welcome. How gratifying it would be if one could say "cure" instead of "hope," but that transition remains only a possibility.

The efficiency of radioactive gold in palliation as shown in the author's Table V indicates that among 23 patients, 15 required tapping before gold was administered, while only 5 needed to be tapped after the administration of gold. So much relief from the annoying symptoms of ascites is a worth-while accomplishment. In a report from our Isotope Committee, among 14 patients given palliative treatment, 11 had to be tapped for ascites before gold was given and 6 of them had 1 to 4 paracenteses after the gold treatment. Perhaps the size of the dose, 75 to 150 mc. compared to Dr. Cron's 110 to 224 mc., would account for our less favorable result. On the other hand, other factors should be considered such as the type and extent of the growth. What is the optimum dose? Since none of the patients experienced significant distress from the larger doses, the amount given was justified. It is desirable to give as much radiation as the patient can tolerate. One patient who received only 75 mc. seemed to derive the most benefit. Since there are several pertinent features in the course of that patient it may be worth while to review some of them.

In the first place, her tumor was a pseudomucinous cystadenocarcinoma, a type which Dr. Cron did not have represented. A married woman now aged 38 first noticed a lump in the lower abdomen eleven years ago. The lump gradually enlarged during the next three years. Her physician reported that eight years ago a bilateral cystadenoma of the ovary was removed. One of the cysts involved a ureter and she lost one kidney as a result. When she came to me in 1951, which was seven years after she had first noticed the lump, her main complaint was rapid enlargement of the abdomen. At laparotomy 7 L. of clear pseudomucinous fluid was removed. Implantations were observed in the peritoneum, omentum, and liver. Lymphatic glands were not enlarged. Biopsies taken from the numerous nodules in the pelvis were reported to be metastatic papillary adenocarcinoma. After laparotomy

the patient was comfortable for six months. Ascites returned and ten months later (in September, 1951) 6 L. of yellowish ascitic fluid was withdrawn and 75 mc. of radioactive gold in 50 c.c. normal saline was instilled into the peritoneal cavity. Kept on a low-salt intake, she was reasonably comfortable for a year when the ascites returned. The nodules in the pelvis could no longer be felt eighteen months after the administration of gold. Two years after the gold treatment a laparotomy was performed because some difficulty was experienced when paracentesis was attempted. The peritoneal cavity contained 6 L. of dark-brown fluid. The peritoneum was 3 mm. thick and its smooth surface was stained dark brown. Microscopic section of the peritoneum showed dense fibrosis with infiltration of large numbers of pigment-filled macrophages. The surface of the parietal peritoneum was covered by tall columnar cells with a slight papillary tendency in some areas. The visceral peritoneum was smooth and not stained. No evidence of growth remained in the pelvis or on the viscera. For the next year the patient remained well and ascites was negligible. In August, 1954, she became acutely ill with perforation of the ileum. At the emergency operation the same condition of the parietal peritoneum was noted and no evidence of growth on the viscera. Since then there has been no more ascites; she has gained 40 pounds and states that she feels the best she has in years.

Whether segregation of the gold was in any way responsible for the perforation remains a question. The perforation occurred two years after the administration of gold.

Since patients with pseudomyxoma peritonaei live for years, one hesitates to attribute too much value to the radioactive gold in this instance. It is now nearly four years since she had the gold and eleven years since the tumor was first noticed. Of all our patients treated palliatively, this one seems to have been the most benefited.

DR. ROGER SCOTT, Cleveland, Ohio.—We have had about the same experience as Dr. Cron with radioactive gold. We use approximately 125 mc. and have noticed an apparent reduction in the number of subsequent paracenteses. The total number of patients approximates the series of the essayist. One unusual complication in our series is worthy of comment; about 80 per cent of our patients died of intestinal obstruction, which seems contrary to the usual course of the disease. One of our patients informed us of an interesting and new radiation hazard, if we can believe the story. After discharge from the hospital she was stopped by a radar patrol car, looking for something that was jamming their radar.

DR. CRON (Closing).—The dosage was arrived at on a trial and error basis and raised as high as was felt safe. In the unfavorable comments from physicians we had one who said that the patient's subsequent course was complicated by bowel perforation. This has some relationship to Dr. Scott's comments on intestinal obstruction. One thing we have learned, especially when treating patients with ascites, is not to remove all of the fluid; leave some in the peritoneal cavity. As far as possible prevent pocketing of the radiogold because when you get a high concentration in a small area then complications arise.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

The American Journal of the Medical Sciences

Vol. 228, No. 5, November, 1954.

Chambers: Anorexia, Irritability, and Convulsions: Evidences of Subdural Hematoma in Infancy, p. 540.

Subdural hematomas are more common in infants than is generally appreciated. They have serious sequelae, such as brain atrophy, mental retardation, and death. Birth trauma is often a cause. Any infant "who is not doing well in spite of adequate and conscientious care should be suspected of subdural hematoma." There are no constant signs, and remissions may occur. In about one-third of the cases, there may be enlarging heads with bulging fontanelles; fever is common. Other signs may be hyperreflexia, anemia, abnormal optic fundi, and paralysis. Bilateral subdural taps, through the anterior fontanelle, will establish the diagnosis. Characteristically, the fluid volume is increased and the protein content is high.

Treatment by drainage alone is not adequate. Comparatively large craniotomy is indicated. Not only should the fluid be removed, but the constricting subdural membranes should be excised. The author reports 5 cases, as representative of his series, in which such treatment was successful.

LEON C. CHESLEY, M.D.

Eckenhoff and Funderburg. The Opiate Antagonists Nalorphine and Levallorphan, p. 546.

Patients who underwent minor surgery were given large doses of Nisentil or Metopon before and during nitrous oxide anesthesia. At the end of the operation the respiratory rate and volume and the blood pressure were measured. Nalorphine was then given intravenously and the measurements repeated at short intervals. The depression in respiratory rate and volume was abolished in one to two minutes. There was no consistent effect upon the pulse rate and blood pressure. A variable analeptic effect was observed. In similar experiments, Nalorphine and Levallorphan successfully countered the respiratory depression induced by Levorphan and morphine. Nalorphine alone is a potent depressing drug.

Nalorphine, in doses of 0.1 to 0.4 mg., was injected into the umbilical cord veins of 26 infants who had apnea, cyanosis, and poor muscle tone. These infants may have been depressed by overdoses of opiates. The interval from delivery to injection varied from 3

*Titles preceded by an asterisk are abstracted below.

to 22 minutes. The response was graded as excellent in 23, fair in 2, and zero in 1. Neonatal depression can be countered by injecting Nalorphine intravenously in parturient women who are overly depressed.

LEON C. CHESLEY, M.D.

Vol. 228, No. 6, December, 1954.

*Sherman, Alfred I., and Arneson, A. N.: Carcinoma of the Endometrium, p. 701.

Sherman and Arneson: Carcinoma of the Endometrium, p. 701.

In the period from 1930 to 1948, 260 cases of primary carcinoma of the corpus were accumulated for five-year survival study at the Barnes and the Barnard Free Skin and Cancer Hospitals. Radiation therapy alone was used in 112 cases, surgery alone in 57, and combined treatment in 91. The operation usually was complete hysterectomy with removal of both oviducts and ovaries and a small segment of the vagina. In the combined method, the radiation was given prior to operation. The five-year survival rates were: radiation alone, 26 per cent; surgery alone, 70 per cent; combined therapy, 72.5 per cent. In early cases, the survivals were 39, 78, and 83 per cent, respectively. In late cases they were 15, 42, and 59 per cent, respectively. "Early cases" are defined as those in which the uteri were smaller than the size of a 2½ months' gestation, or less than 12 cm. in depth. Evidence of extension of the disease outside the uterus threw the patient into the "late" group, regardless of the size of the uterus.

Well-differentiated carcinomas carried a better prognosis than anaplastic ones. The five-year survivals were: radiation therapy alone, 32 per cent for differentiated carcinomas and 17 per cent for anaplastic ones; surgery alone, 94 and 35 per cent, respectively; combined therapy, 81 and 59 per cent, respectively.

In the patients who had preoperative radiation therapy, the five-year survivals were 66 per cent in those who were "controlled" as judged histologically and 34 per cent in those who were not. There was no difference between the well-differentiated and anaplastic carcinomas in regard to percentages "controlled" by radiation.

The relative prognoses were: early, well-differentiated, 84 per cent five-year survival; early, anaplastic, 44 per cent; advanced, well-differentiated, 41 per cent; advanced, anaplastic, 18 per cent; whole series (260 cases) 50.2 per cent.

If radiation is to be used, radium should be supplemented with external roentgen therapy. In 43 cases the total radiation was calculated. The five-year survival rates, in relation to dose, were: less than 4,000 r, 28 per cent; 4,000-5,500 r, 41 per cent; 5,500 to 7,000 r, 67 per cent; 7,000 plus r, 86 per cent. Radium treatment should include both intrauterine and intravaginal applications. Multiple capsules should be packed into the uterus whenever possible. Hysterectomy should be done in all operable patients and the use of preoperative radiation will improve the prognosis.

LEON C. CHESLEY, M.D.

Vol. 229, No. 1, January, 1955.

Rogers, Fred B., and Lansbury, John: Atrophy of Auricular and Nasal Cartilages Following Administration of Chorionic Gonadotrophins in a Case of Arthritis Mutilans With the Sicca Syndrome, p. 55.

*Hulet, William H.: The Sodium, Potassium and Chloride Content of the "200 Mg. Sodium Diet," p. 85.

Hulet: Sodium, Potassium and Chloride Content of the "200 Mg. Sodium Diet," p. 85.

Thirteen separate menus were prepared, each calculated from tables to contain 200 mg. of sodium. The actual sodium content, by analysis, varied from 304 to 812 mg. The Kempner rice and fruit diet, calculated to contain 26 mg. of sodium, actually had 169 mg.

LEON C. CHESLEY, M.D.

The British Medical Journal

Vol. II, October 9, 1954.

Tennent and Black: Surgical Induction of Labour in Modern Obstetric Practice, p. 833.

Surgical induction of labor by artificial rupture of the membranes appears to be a valuable asset in the treatment or prevention of some of the common complications of pregnancy.

Amniotomy was performed in 1,585 cases and was rarely supplemented by medical induction. The principal indications for this procedure included prolonged pregnancy, hypertensive toxemia, contracted pelvis, large fetus, and previous cesarean section. Maternal mortality was 0.06 per cent. The corrected fetal mortality was 2.3 per cent and the cesarean section rate was 2.9 per cent. Failed induction was determined by a latent period of over 72 hours, which occurred in 9 per cent of the primigravidas and in 12 per cent of the multiparas. With the liberal administration of antibiotics and chemotherapy there was no reverse in the morbidity.

The discussion of induction of labor in cases of previous cesarean section was most interesting. There were 39 patients in this category. The one maternal death of the overall series was in this group. She was delivered by repeat section after unsuccessful attempt at induction. Her death was attributed to postoperative complications, unrelated to the induction. This group had no fetal mortalities. Four patients were delivered by cesarean section, while the other 35 had uneventful vaginal parturitions. All of these cases were carefully selected and induction was attempted, provided the previous indications for section did not exist.

The authors inferred that surgical induction in selected cases would contribute to decreasing the maternal risk and fetal wastage. However, they consider that this method used in conjunction with Pitocin drip would improve the efficiency.

ARTHUR PERELL, M.D.

MacLennan: Management of Labour in the Contracted Pelvis, p. 837.

In fifty years the incidence of pelvic contraction among the obstetrical patients of the Glasgow Royal Maternity Hospital has decreased from 27 per cent to 4 per cent. The standard for contraction is a true conjugate of less than 10 cm. Whenever this was discovered there were other evidences of contraction elsewhere in the pelvis which were considered to be rachitic in etiology.

The author reviews previous modes of treatment in this clinic. This emphasizes the eradication of craniotomy with its replacement by cesarean section. He advocates that the pendulum has swung too far and perhaps premature induction may be considered in place of abdominal delivery. A better term for the proposed method would be "trial induction of premature labor."

The criteria must take into account the size of the baby. For although the premature may easily negotiate the pelvis, it may, if too small, succumb to prematurity. Antibiotics should be utilized as prophylaxis against infection. The obstetrician must be prepared for immediate surgical intervention with the first evidence of further complication.

This procedure has merit but must be reserved for those with precise obstetrical judgment and sufficient experience.

ARTHUR PERELL, M.D.

Vol. II, October 30, 1954.

Durham, M. P., Shooter, R. A., and Curwen, M. P.: Failure of Sulphonamides to Prevent Urinary Infections After Vaginal Surgery, p. 1008.

Wickes, Ian G.: Foetal Defects Following Insulin Coma Therapy in Early Pregnancy, p. 1030.

Vol. II, November 6, 1954.

Dalton, Katharina: Similarity of Symptomatology of Premenstrual Syndrome and Toxaemia of Pregnancy and Their Response to Progesterone, p. 1071.

Allan, James: Leukaemia and Pregnancy, p. 1080.

Dawson, John, and Mitchell, P. R.: The Value of Radiology in Ante-partum Haemorrhage, p. 1085.

Vol. II, November 20, 1954.

Jefferiss, F. J. G.: The Doubtful Syphilitic Blood Test in Pregnancy, p. 1200.

Vol. II, November 27, 1954.

Cappell, D. F., Hendry, E. B., Hutchinson, H. E., and Conway, Hugh: A New Carbohydrate-Iron Haematinic for Intramuscular Use, p. 1255.

*Scott, J. M., and Govan, Teleford: Anaemia of Pregnancy Treated With Intramuscular Iron, p. 1257.

Scott and Govan: Anaemia of Pregnancy Treated With Intramuscular Iron, p. 1257.

Various investigators as early as 1893 have debated as to the efficacy of the administration of iron by the intramuscular route. Results differed and it was generally agreed that further trials had to await the development of a less toxic preparation. This report is an evaluation of Imferon, a dextran iron complex, which may be utilized intramuscularly or intravenously.

Studies were performed on 50 anemic pregnant women. Anemia was grouped as mild in 14 cases where the recorded hemoglobin was 9 to 9.5 Gm. per cent, moderate in 28 with hemoglobin ranging from 8 to 8.9 Gm. per cent, and severe in 8 where the hemoglobin was less than 8 Gm. per cent. Other hematologic determinations included reticulocytes, hematocrits, and in selected cases serum iron assay.

Doses was given daily equivalent to 100 mg. of elemental iron or twice-weekly doses each equivalent to 250 mg. of elemental iron. Response depends upon volume rather than frequency of administration. The hemoglobin increase averaged 0.3 Gm. for every 100 mg. of elemental iron injected. This improvement is equivalent to the response with intraveinous saccharated oxide iron preparations. One precaution to be taken is to administer the medication by deep injection as skin pigmentation may result from superficial injections.

The potentiality of this convenient mode of iron therapy is worth further consideration. If the results obtained by the author are found to be consistent when controlled and significant numbers of patients are tested, this will prove a valuable adjunct.

ARTHUR PERELL, M.D.

Vol. II, December 11, 1954.

Loeser, Alfred A.: A New Therapy for the Prevention of Post-Operative Recurrences in Genital and Breast Cancer, p. 1380.

Current Researches in Anesthesia and Analgesia

Vol. 33, No. 5, September-October, 1954.

*Mann, John: Resuscitation of the Newborn, a Method and a Machine, p. 289.

*Morris, George, and Moyer, John: Clinical Experience With Chlorpromazine in Spinal Anesthesia, p. 340.

Seldon, Thomas H.: Plasma Expanders, p. 346.

Mann: Resuscitation of the Newborn, p. 289.

The causes of asphyxia neonatorum are reviewed in this paper and the indications for more active resuscitative efforts are outlined. If spontaneous respiration does not ensue, endotracheal intubation under direct laryngoscopy is then accomplished with the use of a metal catheter. The intratracheal catheter is then directly attached to a resuscitator apparatus which is at first adjusted to aspirate mucus, followed by alternating positive pressure (12 mm. Hg) and negative pressure (8 mm. Hg) oxygen at a rate of 10 to 15 per minute. The machine described by the author is praised for its simplicity in construction with resultant dependability and freedom from breakdown.

Dr. Mann is opposed to the use of positive pressure in excess of 12 mm. Hg because of the implied possibility of producing lung rupture and pneumothorax. No evidence is advanced in this article, however, that higher pressures lasting only an instant would result in this catastrophe.

The author's approach in the management of asphyxia neonatorum represents a positive step toward the logical solution of this problem and will help to eliminate the antiquated procedures still in use.

GERALD S. STOBER, M.D.

Morris and Moyer: Chlorpromazine in Spinal Anesthesia, p. 340.

The authors successfully treated 21 of 23 patients who developed nausea and retching under spinal anesthesia by the administration of 25 mg. of chlorpromazine intravenously. In all of the successful cases the response was immediate.

Patients pretreated with 12.5 mg. chlorpromazine intravenously failed to develop nausea or retching following traction on the stomach at laparotomy, although this procedure induced this response prior to medication.

The antiemetic properties of chlorpromazine are consequently substantiated by this work. The previously observed side reactions of hypotension and sedation were noted also in this group of cases.

GERALD S. STOBER, M.D.

Deutsche Medizinische Wochenschrift

Vol. 79, No. 2, October 15, 1954.

Foellmer, W., and Rother, M.: The Fate of Mother and Child Following Delivery Out Wedlock, p. 1556.

*Stoll, P., and Bach, H. G.: The Significance of Postmenopausal Bleeding, p. 1559.

Stemmer, W.: Tampons and the Physiology of the Vaginal Contents, p. 1562.

Stoll and Bach: Significance of Postmenopausal Bleeding, p. 1559.

Of 574 cases of postmenopausal bleeding seen in three years (postmenopausal bleeding is here defined as bleeding per vaginam occurring at least two years after menopause), 45 per cent were malignant. Of the malignant cases, 56 per cent were carcinoma of the cervix and 35 per cent were carcinoma of the fundus. Bleeding due to malignancy occurred mainly in the age group between 55-59 years (29.5 per cent); bleeding from benign cases occurred chiefly in the age group between 50-59 years (29.7 per cent). There is also a correlation between the onset of bleeding and the time elapsed since the menopause. Most benign bleeding occurs within the first five years.

All postmenopausal bleeding should be thoroughly investigated with curettage, biopsy of the cervix, and, if adnexal masses are found, laparotomy.

WALTER F. TAUBER, M.D.

Vol. 79, No. 43, October 22, 1954.

*Heberer, H.: Pregnancy Beyond 40 Weeks, p. 1594.

Heberer: Pregnancy Beyond 40 Weeks, p. 1594.

The author feels that pregnancy prolonged beyond term carries considerable fetal risk, aside from fetal skeletal changes of postmaturity. He demonstrates that weight gain in pregnancy continues to just about the two hundred eightieth postmenstrual day and that this is followed by stable weight and, in turn, by weight loss. In 3,000 consecutive deliveries, 96 went over term with a fetal mortality of 10.4 per cent, compared to about 2 per cent over all. The author feels, therefore, that labor should be induced in patients who go over term. Great care must be taken in the accurate determination of the expected date of confinement, using careful history taking, determination of quickening, and close supervision of weight.

WALTER F. TAUBER, M.D.

Vol. 79, No. 51, December 17, 1954.

Leinzinger, E., and Ribitsch, F.: The Oral Induction of Labor with Methylergotamine, p. 1899.

Edinburgh Medical Journal

Vol. 61, November, 1954.

*Winchester, G., and Brown, R.: Caesarean Section With Special Reference to Subsequent Childbearing, p. 63.

Winchester and Brown: Caesarean Section With Special Reference to Subsequent Childbearing, p. 63.

Of 1,008 primigravid women who were delivered by cesarean section, 245 were seen during subsequent pregnancies and of 478 multiparous women, 88 were seen during later pregnancies. More than one-third of the primiparas and nearly one-half of the multiparas have later had one or more vaginal deliveries (136 women, 189 babies). This was accomplished with only 2 neonatal deaths if one excludes instances of fetal abnormality, prematurity, and accidents of pregnancy, thereby reducing the crude death rate of 12 per cent. There was no maternal mortality. Both in and out of the present series 13 instances of rupture of the uterus during succeeding pregnancies were seen, but only one patient had had a previous lower uterine segment operation as opposed to the classical operation. Two hundred sixty-seven women had a second abdominal delivery and 43 had a third operation. Most of these were performed because of contracted pelvis or disproportion (58 per cent) or "previous caesarean section" (25 per cent). The authors stress that a full and careful reassessment should be made before advising a second cesarean operation and that the indications for the classical cesarean section should be severely restricted because of the danger of subsequent rupture of the uterus.

DAVID M. KYDD, M.D.

Fertility and Sterility

Vol. 5, November-December, 1954.

*Bunge, R. G., Keettel, W. C., and Sherman, J. K.: Clinical Use of Frozen Semen, p. 520.

Bunge, Keettel, and Sherman: Clinical Use of Frozen Semen, p. 520.

The authors mixed nine parts of normal liquefied human semen with one part of glycerol and placed the treated semen in an insulated box containing dry ice. The slow freezing of the glycerol-treated semen yielded 67 per cent survival of the living spermatozoa in the specimen, even after three months in storage; that is, after quick thawing in a 37° C. water bath, 67 per cent of the originally living spermatozoa were found to survive.

These revived spermatozoa showed no detectable alterations in motility or morphology. Neither glycerol nor refrigeration affected the intensity of the staining reaction of spermatozoa to various dyes.

When previously frozen semen which had been thawed was allowed to cool from room temperature to that of an ordinary refrigerator (4° C.) for one hour, the temporarily immobilized spermatozoa fell to the bottom of the test tube, just as they do when semen is centrifuged. By withdrawing the supernatant fluid, a concentrated specimen of vital spermatozoa was obtained from the bottom of the tube.

The authors used this method to treat four unproductive women with their husbands' specimens of semen. These men, therefore, were represented, the authors believe, by semen of greater potential than that which existed in their original untreated specimens. This was particularly true because the revived concentrated spermatozoa could be used at the most propitious time of the menstrual cycle. All four women became pregnant through the use of frozen thawed semen which was stored from 48 hours to 6 weeks' time. All four babies were normal. The authors did not state whether intercourse was interdicted during the therapeutic insemination.

PAUL TOPKINS, M.D.

Irish Journal of Medical Science

Series 6, No. 344, August, 1954.

*Humphrey, B. M.: Obstetrics in Literature, p. 345.

Humphrey: Obstetrics in Literature, p. 345.

This presentation is a lecture referring to some of the many obstetrical references in the world's literature. The author states that "locked twins" are first reported in Genesis, chapter 38, verses 27 through 30. Additional reference is made to Charles Dickens' "Dombey and Son," in which the death of Mrs. Dombey in the early puerperium is recorded. The author also includes the classic description of a delivery in China as recorded by Pearl Buck, in "The Good Earth."

SCHUYLER KOHL, M.D.

Series 6, No. 345, September, 1954.

Verney, Ernest B.: Water Diuresis, p. 377.

*Doyle, G. D., and McGrath, John: Pregnancy Anaemia Survey, p. 414.

Doyle and McGrath: Pregnancy Anaemia Survey, p. 414.

This communication is a report of the "Pregnancy Anaemia Survey" at the Coombe Lying-in Hospital for the year 1953. This edition of the Irish Journal of Medical Science carries another article on anemia complicating pregnancy. These articles recur almost monthly in this journal, and must reflect the apparent importance of this complication of pregnancy in Ireland. The authors report that 31.4 per cent of the 1,000 patients studied exhibited an anemia during pregnancy. This complication of pregnancy in the present report is least frequently present in those patients in their second, third, or fourth pregnancy. In a primagravida it is next most frequent. From para v upward there appears to be a slight but consistent tendency toward an increase in the incidence of anemia complicating pregnancy. The authors have attempted to correlate the presence or absence of anemia with diet and housing. Their data seem to indicate that as diet and housing go from "good" through "fair and poor" to "bad," anemia goes from an incidence of 30 per cent to 83 per cent. The report likewise shows that the quality of diet and living conditions is related to the expenditure for food. Seventy-eight per cent of those having good diet and living conditions expend the greater amount of money for food, whereas 74 per cent of those who have a bad diet and living conditions are unemployed. The authors correlated the presence or absence of anemia in 476 mothers with whether or not the baby immediately preceding the present pregnancy, was breast fed or not. Regardless of the duration of breast feeding or absence of breast feeding, the incidence of anemia was the same, 44 per cent.

In closing, the authors pointed out that while the incidence of anemia was approximately 30 per cent in the 1,000 patients studied, the incidence of megaloblastic anemia was 0.8 per cent.

SCHUYLER KOHL, M.D.

Series 6, No. 346, October, 1954.

Curtin, Michael: Failure to Breast Feed, p. 447.
Cullen, Robert: Observations on Megaloblastic Anaemias of Pregnancy, p. 463.
Boland, S. V.: Placentography, p. 469.

Journal of the American Geriatrics Society

Vol. 2, No. 12, December, 1954.

Buxton, C. L.: Postmenopausal Bleeding, p. 807.

Vol. 3, No. 1, January, 1955.

Schauffler, Goodrich C.: Significance and Management of Genital Prolapse in the Aged, p. 43.

Journal of the American Medical Association

Vol. 153, No. 3, September, 1953.

*Spies, Thomas D.: Influence of Pregnancy, Lactation, Growth, and Aging on Nutritional Processes, p. 185.

Spies: Influence of Pregnancy, Lactation, Growth, and Aging on Nutritional Processes, p. 185.

The author reports his experiences in the past twenty-five years on certain nutritional processes. He stresses the fact that the problem of aging and illness should be approached as a chemical as well as a clinical problem. Deficiency diseases in human beings develop slowly and are corrected slowly. Frequently there is a point beyond which there is some irreversible change. As a result of his work the author concludes that the following are four essentials for therapy in nutritive failure: (1) diet—adequate calories, adequate protein, vitamins, and minerals in suitable and edible form for the individual person; (2) basic supplement—vitamin A, thiamine, riboflavin, nicotinamide, ascorbic acid, folic acid, vitamin B_{12}, and activator when necessary; (3) additional medication—as indicated for coexisting diseases; (4) natural B complex—dried brewer's yeast powder or liver extract.

Pregnancy, lactation, growth, and aging result in special stresses on nutritional processes of the body. Improper diet is not the sole cause of dietary deficiency diseases; impaired absorption from the alimentary tract, failure of utilization by the tissues, and inadequate storage may be contributing factors.

WILLIAM BERMAN, M.D.

Vol. 156, No. 5, October 2, 1954.

Haynes, D. M.: Occiput Posterior Position, p. 494.

Vol. 156, No. 6, October 9, 1954.

Novak, E. R.: The Menopause, p. 575.
McLennan, C. E.: Reflections on the Physiology of Menstruation, p. 578.
Holmstrom, E. G.: Functional Uterine Bleeding, p. 580.
de Alvarez, R. R.: Amenorrhea, p. 582.

Vol. 156, No. 7, October 16, 1954.

Kavinoky, N. R.: Premarital Medical Examination, p. 692.
Lardaro, H. H.: Spontaneous Rupture of Tubo-Ovarial Abscess Into the Free Peritoneal Cavity, p. 699.

Vol. 156, No. 10, November 6, 1954.

Hanley, B. J.: The Challenge of Dystocia, p. 935.

Vol. 156, No. 14, December 4, 1954.

Holman, E. J.: Medicolegal Aspects of Sterilization, Artificial Insemination, and Abortion, p. 1309.

Vol. 156, No. 16, December 18, 1954.

Potter, E. L.: The Trend of Changes in Causes of Perinatal Mortality, p. 1471.

Judd, G. E.: Management of Labor in Reference to Prevention of Perinatal Mortality, p. 1474.

Taylor, E. S.: The Role of Analgesia and Anesthesia in Fetal Salvage, p. 1481.

Vol. 157, No. 1, January 1, 1955.

Russell, K. P., Maharry, J. F., and Stehly, J. W.: Acute Renal Failure as an Obstetrical Complication, p. 15.

Journal of Clinical Endocrinology and Metabolism

Vol. 15, No. 1, January, 1955.

*Gordon, G. S., Overstreet, E. W., Traub, H. F., and Winch, G. A.: Syndrome of Gonadal Dysgenesis: A Variety of Ovarian Agenesis With Androgenic Manifestations.

*Zarrow, M. X., Holmstrom, E. G., and Salhanick, H. A.: The Concentration of Relaxin in the Blood Serum and Other Tissues of Women During Pregnancy, p. 22.

Gordon, Overstreet, Traub, and Winch: Syndrome of Gonadal Dysgenesis.

Two cases are reported of ovarian agenesis associated with primary amenorrhea, lack of development of primary and secondary sexual characteristics, increased urinary gonadotropin titer, short stature, rudimentary uterus but enlarged clitoris, hirsutism, and android pelvis. Exploratory laporatomies were perfomed on both patients to confirm the diagnosis. Portions of the ovarian anlagen were removed and examined microscopically. Islands of cells suggestive of hilar cells were found and it was suggested that the virilizing effects may have been caused by androgen production by these cells.

J. EDWARD HALL, M.D.

Zarrow, Holmstrom, and Salhanick: Concentration of Relaxin in the Blood Serum and Other Tissues of Women During Pregnancy, p. 22.

Relaxin is a hormone produced during pregnancy. It has not been found in males and nonpregnant females. The blood serum levels of relaxin were determined quantitatively in normal women throughout pregnancy and at parturition. Several pregnancies complicated by pre-eclampsia and diabetes were studied. Relaxin was found as early as the seventh to the tenth week of pregnancy and the amount increased as the pregnancy progressed, and remained at a plateau level during the last few weeks. The level fell precipitously at delivery and no relaxin was found twenty-four hours after delivery.

Relaxin was found in varying amounts in placental extracts. Amniotic fluid and the myometrium contained no relaxin. The source of relaxin in women is not known.

It is suggested that relaxin may aid in the development of the mammary gland, uterine contractions, decidual reaction, dilatation of the uterine cervix, and possibly relief of the anemia of pregnancy.

J. EDWARD HALL, M.D.

Journal of Obstetrics and Gynaecology of India

Vol. 3, No. 3, March, 1953.

*Satur, D. M.: Parasitic Ovarian Tumors, p. 242.

Satur: Parasitic Ovarian Tumors, p. 242.

The author reports a case of a parasitic dermoid cyst of the ovary associated with pregnancy. The view of most of the authors as to the etiology of avulsion is that torsion, leading to adhesion to the surrounding structures associated with simultaneous weaning from the ovarian blood supply as a result of necrosis of the pedicle, is the most common factor in the amputation of the ovarian cyst. During pregnancy the upward push of the pregnant uterus results, in the course of time, in upward stretching with avulsion of the cyst from the ovary. Pedicle formation and torsion are conspicuous by their absence. The author warns that, in abdominal tumors of unknown origin and especially in tumors of the omentum, a possibility of spontaneous amputation of a dermoid cyst of the ovary should be kept in mind.

WILLIAM BERMAN, M.D.

Vol. 5, No. 1, September, 1954.

De Sa, H.: Some Observations on Double Uterus With Special Reference to Labour, p. 1.

Tampan, R. K. K., and Thankam, M.: Painless Childbirth by the Use of Intravenous Ethyl Alcohol and Pitocin Drip, p. 13.

Menon, M. K., Krishna: Anaemia in Pregnancy With Special Reference to Treatment, p. 17.

Raj, Padma: Folic Acid With and Without Oral Vitamin B_{12} in Treatment of Macrocytic Anaemia in Pregnancy, p. 33.

Rajam, R. V.: The Role of the Obstetrician in the Control of Syphilis, p. 45.

Dutta-Choudhuri, Rebati, and Basu, Swadesh: Primary Carcinoma of the Fallopian Tube, p. 60.

Ajinkya, Y. N.: Record of Cases of Conception in Uterus Bicornis Bicollis, p. 77.

Malkani, Parvati K., and Rajani, Chander K.: Endometrial Biopsy, p. 82.

Menon, M. K. Krishna: Lithopoedion, p. 89.

Reddy, D. Bhaskara, and Bai, B. Surya: Endometriosis of the Vaginal Portion of the Cervix, p. 94.

Moos, Freny B.: Spontaneous Rupture of the Cervix Complicating Expulsion of Vesicular Mole, p. 97.

Journal of Obstetrics and Gynaecology (Northern India)

Vol. 15, No. 8, August, 1954.

Narain, Brij: Eclampsia and Its Treatment in Our Wards, p. 249.

Lata, Jiwan: A Case of Recurrent Eclampsia, p. 269.

Vol. 15, No. 9, September, 1954.

Heilmann, P.: Carcinoma With Special Reference to Carcinoma of the Cervix, p. 281.

Surti, B. S.: Vesico-Vaginal Fistula, p. 289.

Journal of Pediatrics

Vol. 45, No. 2, August, 1954.

Wagner, Edward A., Koch, Carl A., and Jones, Daniel V.: An Improved Indwelling Tube for Feeding Premature Infants, p. 200.

Manson, Gordon: Anomalies of Intestinal Rotation and Mesenteric Fixation, p. 214.

The Lancet

Vol. II, October 30, 1954.

*Ostry, E. I.: Forceps Delivery of the Aftercoming Head, p. 896.

Ostry: Forceps Delivery of the Aftercoming Head, p. 896.

The author discusses the classical maneuvers for breech delivery, paying special attention to mechanisms by which the aftercoming head is delivered.

The problem of maintaining flexion of the head while the trunk is held in extension is gone into with regard to the dangers inherent from simulated flexion, and extension of the head, in the usual method of applying forceps.

A method for applying forceps to the aftercoming head is then described which will overcome these difficulties.

The forceps are applied to the head over the shoulders with the infant in the Burns-Marshall position; once applied, the forceps are held in the right hand, and the fetal abdomen is supported by the operator's left palm. As traction is exerted on the forceps, flexion of the head is accentuated.

By this method the handles of the forceps act as a barrier preventing extension and promoting flexion so that the smallest diameter of the fetal head presents for delivery.

This appears to be a worth-while maneuver for it offers these two advantages: (1) It is mechanically sound and physiologically correct. (2) No assistant is needed to hold the infant while the forceps are being applied.

The article should inspire obstetricians not yet utilizing the procedure to evaluate its merits.

T. SULLIVAN, M.D.

Vol. II, November 6, 1954.

Discombe, George: The Natural History and Management of Haemolytic Transfusion Reactions, p. 936.

Merivale, W. H. H., and Hunter, Richard: Abnormal Glucose-tolerance Tests in Patients Treated With Sedative Drugs, p. 939.

Baird, I. McLean, and Podmore, D. A.: Intramuscular Iron Therapy in Iron-deficiency Anaemia, p. 942.

Simeons, A. T. W.: The Action of Chorionic Gonadotrophin in the Obese, p. 946.

Vol. II, November 13, 1954.

*Bentley, J. F. R., and Waterston, D. J.: Recovery From Meconium Peritonitis, p. 990.

Bentley and Waterston: Recovery From Meconium Peritonitis, p. 990.

Two successfully treated instances of meconium peritonitis are reported. The first, in an infant operated on on the first day of life, was caused by a volvulus. The second, an instance of the more chronic form of the disorder, had a congenital atresia with cyst formation. This patient was operated on on the sixth day of life.

In the first instance the terminal ileum, cecum, appendix, and ascending colon were removed and in the second, 12 cm. of the ileum. In both instances the babies seemed to be normal six months after the operations.

Though the mortality remains high, the authors believe that the now possible skillful operative and postoperative treatment will permit a greater survival rate. The literature is discussed briefly and 14 references are given.

DAVID M. KYDD, M.D.

Vol. II, November 20, 1954.

*Apley, J., Laurance, B., and MacMath, I. F.: Snuffles in the Newborn, p. 1048.

Apley, Laurance, and MacMath: Snuffles in the Newborn, p. 1048.

During the first two weeks of life, 2.6 per cent of infants develop snuffles. The condition lasts 2 to 7 days, occasionally 14 days or longer. Feeding difficulties, suffocative rhinitis, stridor, and mouth breathing were the chief complications. Infants with severe pulmonary infection sometimes had a history of snuffles, but no instances of serious pneumonitis were seen in the present series. Usually the discharge was serous, occasionally it became purulent, rarely sanguineous. No etiology for the condition was discovered but the incidence rises when the infants are exposed to infection. No cases were due to syphilis.

DAVID M. KYDD, M.D.

Vol. II, November 27, 1954.

Nabarro, J. D. N.: The Use of Corticotrophin Gel as a Test of Adrenal Cortical Function, p. 1101.

Brudenell, J. M.: A Cervical Biopsy Knife, p. 1110.

Vol. II, December 4, 1954.

*Higgins, L. G.: Prolonged Pregnancy, p. 1154.

Higgins: Prolonged Pregnancy, p. 1154.

An instance of prolonged pregnancy (389 days) and anencephaly is reported together with a brief review of the literature (9 references).

DAVID M. KYDD, M.D.

Vol. II, December 11, 1954.

Holmes, J. M.: The Use of Continuous Intravenous Oxytocin in Obstetrics, p. 1191.

Vol. II, December 18, 1954.

*Cramond, W. A.: Psychological Aspects of Uterine Dysfunction, p. 1241.

*Jennison, R. F., and Ellis, Helen R.: Intramuscular Iron. A Clinical Trial in Pregnancy, p. 1245.

Cramond: Psychological Aspects of Uterine Dysfunction, p. 1241.

A series of 50 patients who had had severe uterine dysfunction was matched case for case in terms of age, height, and social class with a series of 50 control patients whose labor had been normal. In all the patients with dysfunction the labor lasted more than twenty-four hours, in most more than forty-eight. Forty-seven of the controls were delivered within twenty-four hours. Analysis of information obtained during interviews disclosed no significant differences between the two series as regards neuroticism in childhood; sibling rivalry; school, social, and work records; adjustment to marriage and fertility.

A "dysfunction temperament," consisting of a tendency toward, or suggestive symptoms of, peptic ulcer, little overt anxiety, little tremor or sweating as expressions of anxiety, and a bias was described. This temperament was found in 54 per cent of the cases of dysfunction compared with 12 per cent of the controls.

The conclusion is that uterine dysfunction is of multiple etiology and that psychiatric methods of prediction and prevention in the antenatal period would have no effect on the occurrence of uterine dysfunction.

DAVID M. KYDD, M.D.

Jennison and Ellis: Intramuscular Iron. A Clinical Trial in Pregnancy, p. 1245.

Eighty-one pregnant patients were treated with a dextran-iron complex given intramuscularly and containing 50 mg. of iron per ml. After a few preliminary test doses of 2 ml. daily, the dosage was increased to 5 ml. daily or on alternate days. The total dose was estimated by the formula:

$$\frac{100 - \text{observed Hb\%}}{10} \times 250 + 500 \text{ mg.}$$

Group I (63 patients) received this dose and Group II (18 patients) received a standard dose of 500 mg. of iron in two injections. In Group I the mean initial hemoglobin was 9 Gm. per cent and rose to 12 Gm. per cent in six weeks. In Group II the increase in hemoglobin was less and additional iron was required later in the pregnancy to avoid a renewed fall in hemoglobin. The extent and speed of response are satisfactory when compared to previous reports of the effect of intravenous iron in pregnancy. Too few untoward effects from these intramuscular injections were encountered. No induration or abscess formed but a few enlarged and tender inguinal lymph glands

appeared. Unless the injection was given deeply some staining was seen. Slight pyrexia, headache, nausea and vomiting occurred. One patient developed a transient rash and one severe vomiting with syncope. The estimated utilization of the complex (51 mg. of iron raised the hemoglobin level by 1 per cent) is discussed in relation to the other advantages of intramuscular injection over treatment by intravenous injection of the saccharated iron oxide in patients who are intolerant of oral iron.

DAVID M. KYDD, M.D.

Vol. I, January 1, 1955.

*Maher, R. M.: Relief of Pain in Incurable Cancer, p. 18.

Hargreaves, G. R.: Obstetrics and Psychiatry, p. 39.

Maher: Relief of Pain in Incurable Cancer, p. 18.

Intrathecal phenol (1.0 to 1.7 ml. of 1 part phenol in 18 to 20 parts of glycerin well mixed with 0.1 ml. water per milliliter) was injected in 37 cases of incurable cancer (of the cervix 15 patients, rectum 5, genitourinary tract 2, stomach 2, brachial and cervical region 6, and of the lung 7 patients). Long-lasting relief of pain was obtained in 29 patients. Success depended upon whether single or combined nerve groups were involved.

DAVID M. KYDD, M.D.

Vol. I, January 8, 1955.

*Bayliss, R. I. S., Browne, J. C. McC., Round, Brenda, and Steinbeck, A. W.: Plasma-17-Hydroxycorticosteroids in Pregnancy, p. 62.

Bayliss, Browne, Round, and Steinbeck: Plasma-17-Hydroxycorticosteroids in Pregnancy, p. 62.

Samples of blood were analyzed for 17-hydroxycorticosteroids at monthly intervals from 30 women during the course of normal pregnancy, and at various intervals up to as long as 56 days after delivery. In 15 instances samples of cord blood were obtained. At the third month the mean level of 10 μg. per cent is the same as that found in nonpregnant women. Thereafter the level rises steadily, the highest level reached being 24 μg. per cent during the last month of gestation. The amount found in cord blood was even higher (27 μg per cent). Subsequent to delivery after remaining high for one day the level steadily fell, reaching normal usually by the eighth day. While the level of 17-hydroxycorticosteroids followed this general course, individual patients, however, showed considerable variation from the mean values. The nature and origin of the material formed during pregnancy are discussed and the possibility that increased formation of 17-hydrocorticosteroids in pregnancy may explain the betterment of rheumatoid arthritis and the exacerbation of diabetes mellitus that may occur during pregnancy is mentioned.

DAVID M. KYDD, M.D.

Wiener Klinische Wochenschrift

Vol. 66, No. 35/36, September 3, 1954.

Schoenbauer, L., and Schmidt-Ueberreiter, E.: Is Castration Justified in Carcinoma of the Breast? p. 628.

Halter, G.: The Formation of an Artificial Vagina When the Internal Genitalia Are Present, p. 668.

Vol. 66, No. 37, September 17, 1954.

Burkl, W.: Study of the Problem of Post-natal Oogenesis, p. 715.

Vol. 66, No. 39, October 1, 1954.

Politzer, G.: The Present Knowledge of the Development of Human Germ Cells in the Light of Recent Investigations on the Oogenesis in Mammals, p. 747.

Vol. 66, No. 44, November 5, 1954.

Rockenschaub, A.: Workup for Sterility, p. 852.

Vol. 66, No. 45, November 12, 1954.

Froewis, J.: The Surgical Treatment of Sterility in Women, p. 871.

Correspondence

Reanalysis of Data Concerning Remote Prognosis in Patients With Functionally Severe Rheumatic Heart Disease in Pregnancy

To the Editors:

Last October we published some of our analyses of data bearing upon the remote prognosis in patients with "functionally severe" rheumatic heart disease in pregnancy (AM. J. OBST. & GYNEC. **68**: 1151, 1954). We compared two groups of patients: Those who did and those who did not have pregnancies subsequent to the one in which the diagnosis of severe cardiac impairment was established. The remote annual death rate was not increased in those having later pregnancies and we concluded that later pregnancies, even with their own hazards, did not increase the death rate. We have reanalyzed the data and it now appears to us that we must modify the conclusion.

In the published analyses, the average annual death rates were calculated by dividing the number of deaths by the total years survived. For both groups we started the count of patient-years (survival) from the time of delivery of the pregnancy that qualified the patient for admission to the series. The only statistical operations were counting and dividing. We recognized a time bias, in that those having later pregnancies had lived long enough to conceive again. We attempted to correct for this by excluding the first 5 years of follow-up.

The new analysis differs in two essential points. (1) We followed the approach that we had used in a similar study of hypertensive disease (AM. J. OBST. & GYNEC. **53**: 851, 1947). For the "Later Pregnancy" group we started the count of patient-years survival at the time of the later conception, rather than at the time of delivery of the pregnancy in which the diagnosis was made. The interval years are credited the "No Later Pregnancy" group. Inasmuch as the two groups appear to be comparable, this adjustment constitutes a severe bias against the "Later Pregnancy" group because, statistically, it deprives these women with marked cardiac impairment and limited life expectancy of an average of three years' survival (38 patients pregnant again; 111.5 accumulated patient-years from delivery to subsequent conception). However, this operation appears to be necessary to offset the time bias alluded to above. (2) Even after this adjustment, the direct comparison of average annual death rates contains a subtle pitfall. Every table in our paper showed a lower remote annual death rate for the "Later Pregnancy" group as compared to the "No Later Pregnancy" cases.

The reanalysis just outlined gives almost identical mortality rates as between the two groups, in every table. The whole follow-up is so long, however, as to obscure what happened in the early years and the average annual death rates are misleading. In the first 6 years, the remote annual death rate for the "Later Pregnancy" group was 82 per 1,000 (in the new analysis), as against 49 per 1,000 for the "No Later Pregnancy" cases. Five fewer deaths would be required in the "Later Pregnancy" group to equalize the rates. We can account for these 5 deaths, for 5 of the 38 women with later pregnancies died in one or another of the 52 later pregnancies. Therefore, our conclusion that the hazards of later pregnancy itself had not increased the death rate is incorrect. Inasmuch as the average annual death rates for the two groups are identical in the long-term follow-up, it appears that these women probably would have died some time during this period of up to 20 years. As Table I shows, the "Later Pregnancy" group had a high mortality in the early years of follow-up, but relatively a very low mortality in the later years. This strongly indicates that those women who died in pregnancy died prematurely.

TABLE I. COMPARISON OF ANNUAL DEATH RATES IN PATIENTS WITH SEVERE RHEUMATIC HEART DISEASE, IN RELATION TO LATER PREGNANCIES

YEARS OF FOLLOW-UP		NO LATER PREGNANCY			LATER PREGNANCY		
		PATIENT-YEARS	DEATHS	ANNUAL DEATH RATE	PATIENT-YEARS	DEATHS	ANNUAL DEATH RATE
1st	3	344.5	17	49	100.0	9	90
2nd	3	247.0	12	49	81.5	6	74
3rd	3	191.0	13	68	52.0	3	58
10-21		227.5	16	70	78.0	1	13
Total		1010.0	58	57	311.5	19	61

In assessing the remote effect of repeated pregnancy, perhaps one could drop the deaths occurring in pregnancy. If this be done, then our conclusion that pregnancy has no remote effect upon the mortality rate would stand. Pregnancy has no effect provided that the patient survives the pregnancy.

We still are of the opinion that the 5 deaths in pregnancy were preventable and that these women would not have died had they sought early care in the cardiac clinic (although one did). This is indicated by recently published experiences of several cardiac clinics for pregnant women, notably Cook County, Dublin National Maternity, Philadelphia Lying-In, and our own.

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